1. Introduction

Introduction
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Blood Pressure
A proficiency in anatomy and physiology is fundamental to any career in the health professions. (credit: Bryan Mason/flickr)

Chapter Objectives

After studying this chapter, you will be able to:

- Distinguish between anatomy and physiology, and identify several branches of each
- Describe the structure of the body, from simplest to most complex, in terms of the six levels of organization
- Identify the functional characteristics of human life

- Identify the four requirements for human survival
- Define homeostasis and explain its importance to normal human functioning
- Use appropriate anatomical terminology to identify key body structures, body regions, and directions in the body
- Compare and contrast at least four medical imagining techniques in terms of their function and use in medicine

Though you may approach a course in anatomy and physiology strictly as a requirement for your field of study, the knowledge you gain in this course will serve you well in many aspects of your life. An understanding of anatomy and physiology is not only fundamental to any career in the health professions, but it can also benefit your own health. Familiarity with the human body can help you make healthful choices and prompt you to take appropriate action when signs of illness arise. Your knowledge in this field will help you understand news about nutrition, medications, medical devices, and procedures and help you understand genetic or infectious diseases. At some point, everyone will have a problem with some aspect of his or her body and your knowledge can help you to be a better parent, spouse, partner, friend, colleague, or caregiver.

This chapter begins with an overview of anatomy and physiology and a preview of the body regions and functions. It then covers the characteristics of life and how the body works to maintain stable conditions. It introduces a set of standard terms for body structures and for planes and positions in the body that will serve as a foundation for more comprehensive information covered later in the text. It ends with examples of medical imaging used to see inside the living body.

Overview of Anatomy and Physiology

By the end of this section, you will be able to:

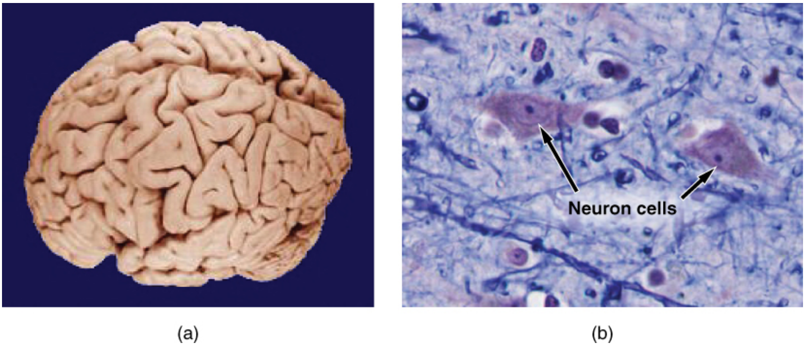
- Compare and contrast anatomy and physiology, including their specializations and methods of study
- Discuss the fundamental relationship between anatomy and physiology

Human **anatomy** is the scientific study of the body's structures. Some of these structures are very small and can only be observed and analyzed with the assistance of a microscope. Other larger structures can readily be seen, manipulated, measured, and weighed. The word "anatomy" comes from a Greek root that means "to cut apart." Human anatomy was first studied by observing the exterior of the body and observing the wounds of soldiers and other injuries. Later, physicians were allowed to dissect bodies of the dead to augment their knowledge. When a body is dissected, its structures are cut apart in order to observe their physical attributes and their relationships to one another. Dissection is still used in medical schools, anatomy courses, and in pathology labs. In order to observe structures in living people, however, a number of imaging techniques have been developed. These techniques allow clinicians to visualize structures inside the living body such as a cancerous tumor or a fractured bone.

Like most scientific disciplines, anatomy has areas of specialization. **Gross anatomy** is the study of the larger structures of the body, those visible without the aid of magnification ([link]**a**). Macro- means “large,” thus, gross anatomy is also referred to as macroscopic anatomy. In contrast, micro- means “small,” and **microscopic anatomy** is the study of structures that can be observed only with the use of a microscope or other magnification devices ([link]**b**). Microscopic anatomy includes cytology, the study of cells and histology, the study of tissues. As the technology of microscopes has advanced, anatomists have been able to observe smaller and smaller structures of the body, from slices of large structures like the heart, to the three-dimensional structures of large molecules in the body.

Gross and Microscopic Anatomy

(a) Gross anatomy considers large structures such as the brain. (b) Microscopic anatomy can deal with the same structures, though at a different scale. This is a micrograph of nerve cells from the brain. LM × 1600. (credit a: “WriterHound”/Wikimedia Commons; credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Anatomists take two general approaches to the study of the body’s structures: regional and systemic. **Regional anatomy** is the study of the interrelationships of all of the structures in a specific body region, such as the abdomen. Studying regional anatomy helps us appreciate the interrelationships of body structures, such as how muscles, nerves, blood vessels, and other structures work together to serve a particular body region. In contrast, **systemic anatomy** is the study of the structures that make up a discrete body system—that is, a group of structures that work together to perform a unique body function. For example, a systemic anatomical study of the muscular system would consider all of the skeletal muscles of the body.

Whereas anatomy is about structure, physiology is about function. Human **physiology** is the scientific study of the chemistry and physics of the structures of the body and the ways in which they work together to support the functions of life. Much of the study of physiology centers on the body’s tendency

toward homeostasis. **Homeostasis** is the state of steady internal conditions maintained by living things. The study of physiology certainly includes observation, both with the naked eye and with microscopes, as well as manipulations and measurements. However, current advances in physiology usually depend on carefully designed laboratory experiments that reveal the functions of the many structures and chemical compounds that make up the human body.

Like anatomists, physiologists typically specialize in a particular branch of physiology. For example, neurophysiology is the study of the brain, spinal cord, and nerves and how these work together to perform functions as complex and diverse as vision, movement, and thinking. Physiologists may work from the organ level (exploring, for example, what different parts of the brain do) to the molecular level (such as exploring how an electrochemical signal travels along nerves).

Form is closely related to function in all living things. For example, the thin flap of your eyelid can snap down to clear away dust particles and almost instantaneously slide back up to allow you to see again. At the microscopic level, the arrangement and function of the nerves and muscles that serve the eyelid allow for its quick action and retreat. At a smaller level of analysis, the function of these nerves and muscles likewise relies on the

interactions of specific molecules and ions. Even the three-dimensional structure of certain molecules is essential to their function.

Your study of anatomy and physiology will make more sense if you continually relate the form of the structures you are studying to their function. In fact, it can be somewhat frustrating to attempt to study anatomy without an understanding of the physiology that a body structure supports. Imagine, for example, trying to appreciate the unique arrangement of the bones of the human hand if you had no conception of the function of the hand. Fortunately, your understanding of how the human hand manipulates tools—from pens to cell phones—helps you appreciate the unique alignment of the thumb in opposition to the four fingers, making your hand a structure that allows you to pinch and grasp objects and type text messages.

Chapter Review

Human anatomy is the scientific study of the body's structures. In the past, anatomy has primarily been studied via observing injuries, and later by the dissection of anatomical structures of cadavers, but in the past century, computer-assisted imaging techniques have allowed clinicians to look inside the living body. Human physiology is the scientific study of the chemistry and physics of the structures

of the body. Physiology explains how the structures of the body work together to maintain life. It is difficult to study structure (anatomy) without knowledge of function (physiology). The two disciplines are typically studied together because form and function are closely related in all living things.

Review Questions

Which of the following specialties might focus on studying all of the structures of the ankle and foot?

1. microscopic anatomy
2. muscle anatomy
3. regional anatomy
4. systemic anatomy

C

A scientist wants to study how the body uses foods and fluids during a marathon run. This scientist is most likely a(n) _____.

1. exercise physiologist
2. microscopic anatomist

3. regional physiologist
4. systemic anatomist

A

CRITICAL THINKING QUESTIONS

Name at least three reasons to study anatomy and physiology.

An understanding of anatomy and physiology is essential for any career in the health professions. It can also help you make choices that promote your health, respond appropriately to signs of illness, make sense of health-related news, and help you in your roles as a parent, spouse, partner, friend, colleague, and caregiver.

For whom would an appreciation of the structural characteristics of the human heart come more easily: an alien who lands on Earth, abducts a human, and dissects his heart, or an anatomy and physiology student performing a dissection of the heart on her very first day of

class? Why?

A student would more readily appreciate the structures revealed in the dissection. Even though the student has not yet studied the workings of the heart and blood vessels in her class, she has experienced her heart beating every moment of her life, has probably felt her pulse, and likely has at least a basic understanding of the role of the heart in pumping blood throughout her body. This understanding of the heart's function (physiology) would support her study of the heart's form (anatomy).

Glossary

anatomy
: science that studies the form and composition of the body's structures

gross anatomy
: study of the larger structures of the body, typically with the unaided eye; also referred to macroscopic anatomy

homeostasis
: steady state of body systems that living organisms maintain

microscopic anatomy
: study of very small structures of the body using magnification

physiology
: science that studies the chemistry, biochemistry, and physics of the body's functions

regional anatomy
: study of the structures that contribute to specific body regions

systemic anatomy
: study of the structures that contribute to specific body systems

Structural Organization of the Human Body

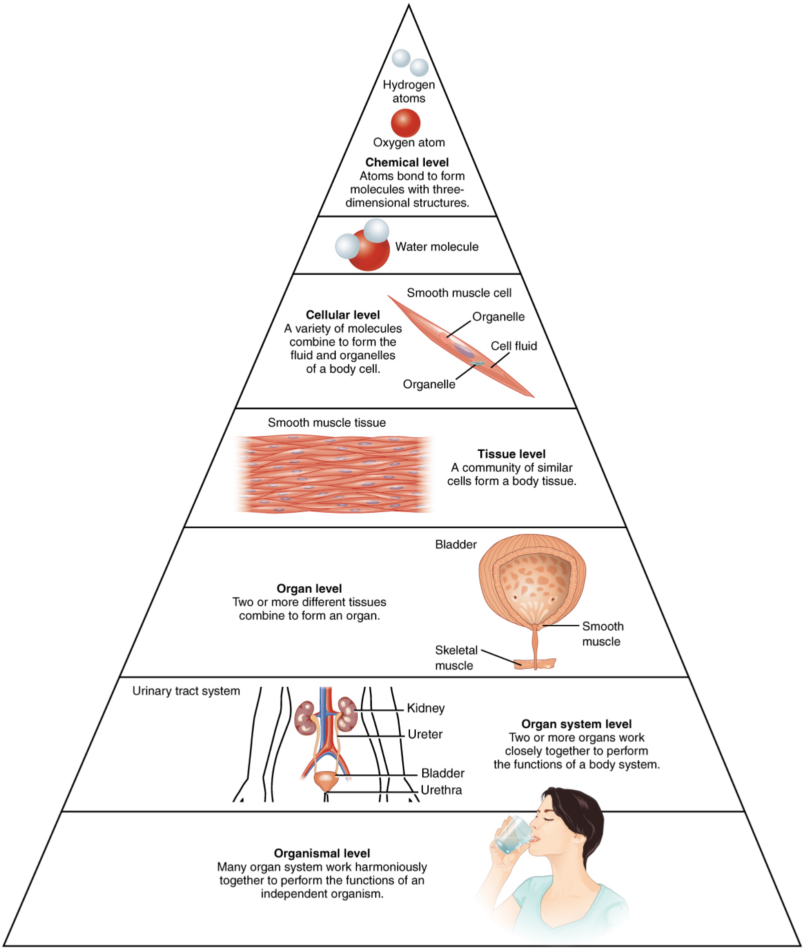
By the end of this section, you will be able to:

- Describe the structure of the human body in terms of six levels of organization
- List the eleven organ systems of the human body and identify at least one organ and one major function of each

Before you begin to study the different structures and functions of the human body, it is helpful to consider its basic architecture; that is, how its smallest parts are assembled into larger structures. It is convenient to consider the structures of the body in terms of fundamental levels of organization that increase in complexity: subatomic particles, atoms, molecules, organelles, cells, tissues, organs, organ systems, organisms and biosphere ([link]).

Levels of Structural Organization of the Human Body

The organization of the body often is discussed in terms of six distinct levels of increasing complexity, from the smallest chemical building blocks to a unique human organism.



The Levels of Organization

To study the chemical level of organization, scientists consider the simplest building blocks of matter: subatomic particles, atoms and molecules. All matter in the universe is composed of one or more unique pure substances called elements, familiar examples of which are hydrogen, oxygen,

carbon, nitrogen, calcium, and iron. The smallest unit of any of these pure substances (elements) is an atom. Atoms are made up of subatomic particles such as the proton, electron and neutron. Two or more atoms combine to form a molecule, such as the water molecules, proteins, and sugars found in living things. Molecules are the chemical building blocks of all body structures.

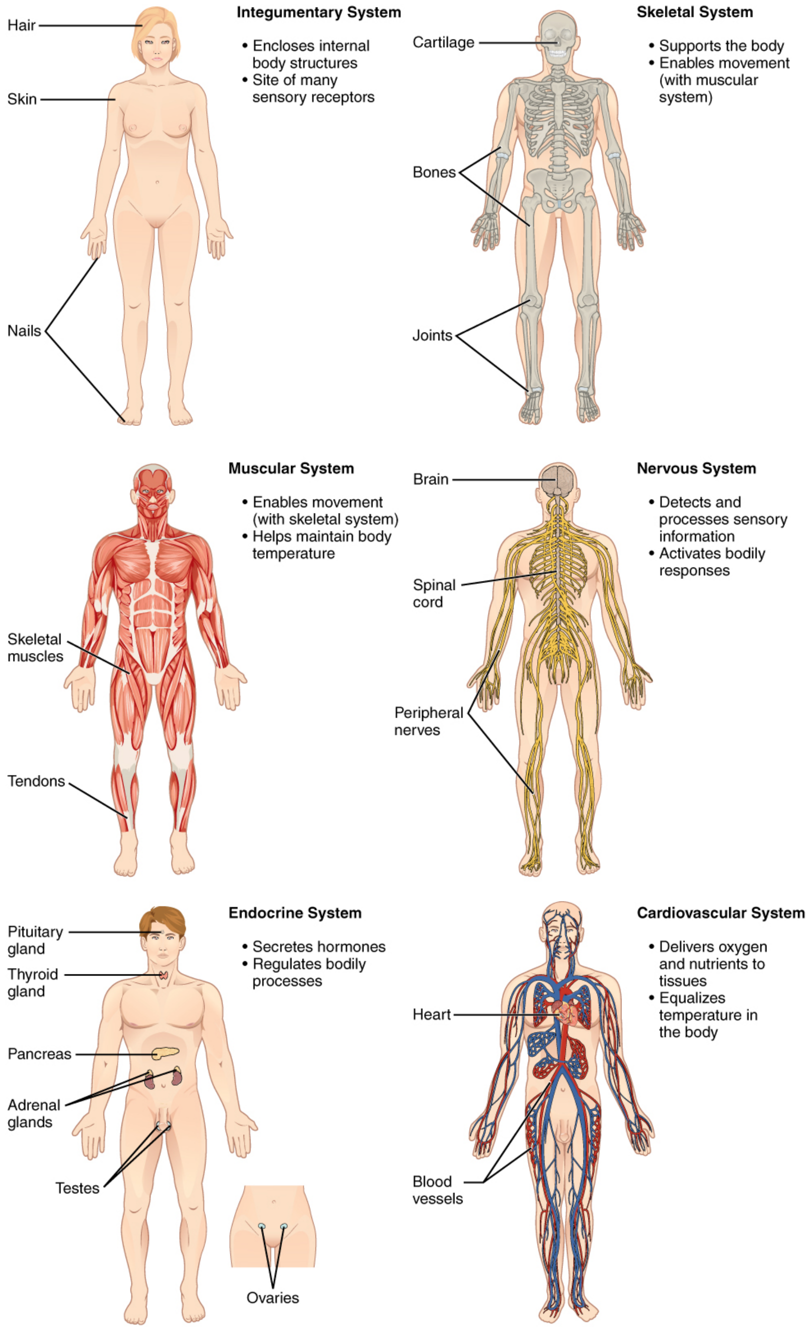
A **cell** is the smallest independently functioning unit of a living organism. Even bacteria, which are extremely small, independently-living organisms, have a cellular structure. Each bacterium is a single cell. All living structures of human anatomy contain cells, and almost all functions of human physiology are performed in cells or are initiated by cells.

A human cell typically consists of flexible membranes that enclose cytoplasm, a water-based cellular fluid together with a variety of tiny functioning units called **organelles**. In humans, as in all organisms, cells perform all functions of life. A **tissue** is a group of many similar cells (though sometimes composed of a few related types) that work together to perform a specific function. An **organ** is an anatomically distinct structure of the body composed of two or more tissue types. Each organ performs one or more specific physiological functions. An **organ system** is a group of organs that work together to perform major functions or meet physiological needs of the body.

This book covers eleven distinct organ systems in the human body ([link] and [link]). Assigning organs to organ systems can be imprecise since organs that “belong” to one system can also have functions integral to another system. In fact, most organs contribute to more than one system.

Organ Systems of the Human Body

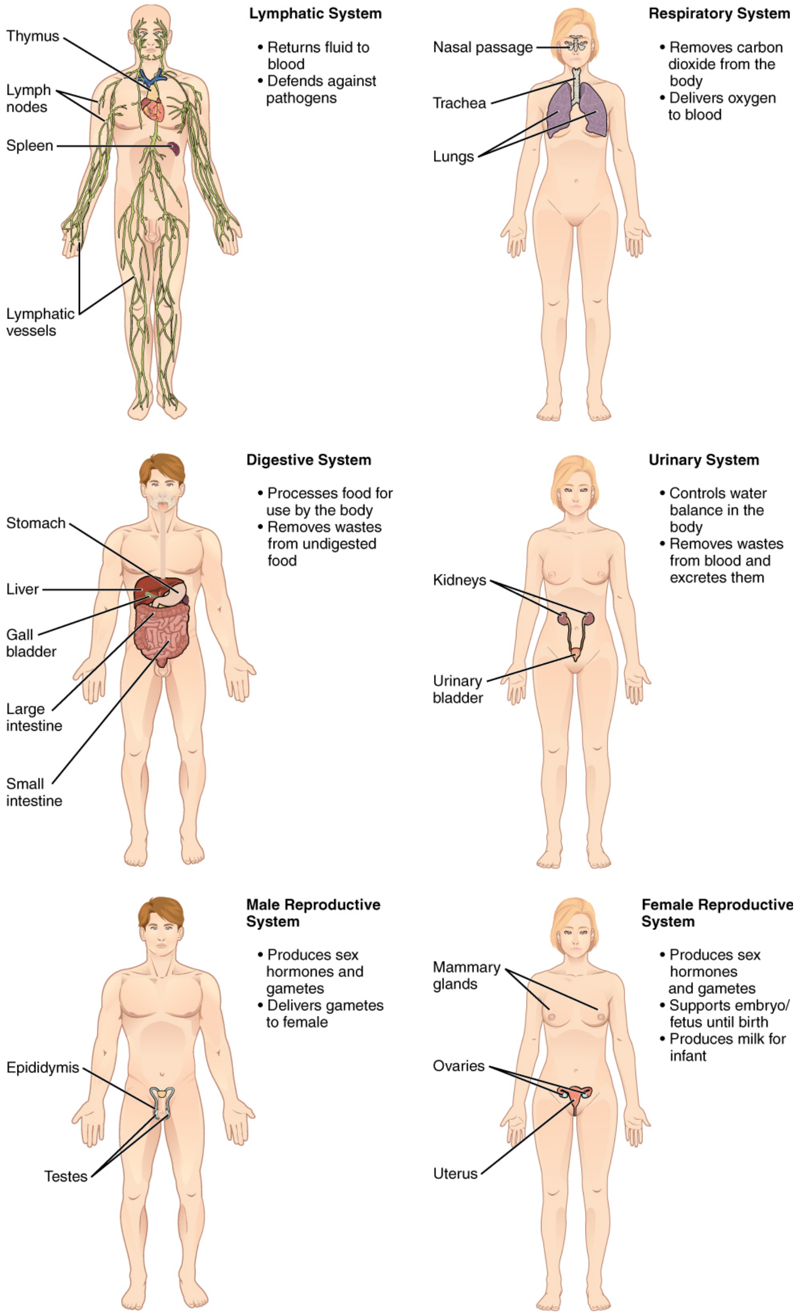
Organs that work together are grouped into organ systems.



Organ Systems of the Human Body (continued)

Organs that work together are grouped into organ

systems.


Lymphatic System
• Returns fluid to blood
• Defends against pathogens
Thymus
Lymph nodes
Spleen
Lymphatic vessels
Respiratory System
• Removes carbon dioxide from the body
• Delivers oxygen to blood
Nasal passage
Trachea
Lungs
Digestive System
• Processes food for use by the body
• Removes wastes from undigested food
Stomach
Liver
Gall bladder
Large intestine
Small intestine
Urinary System
• Controls water balance in the body
• Removes wastes from blood and excretes them
Kidneys
Urinary bladder
Male Reproductive System
• Produces sex hormones and gametes
• Delivers gametes to female
Epididymis
Testes
Female Reproductive System
• Produces sex hormones and gametes
• Supports embryo/fetus until birth
• Produces milk for infant
Mammary glands
Ovaries
Uterus

The organism level is the highest level of organization. An **organism** is a living being that has a cellular structure and that can independently perform all physiologic functions necessary for life. In multicellular organisms, including humans, all cells, tissues, organs, and organ systems of the body work together to maintain the life and health of the organism.

Chapter Review

Life processes of the human body are maintained at several levels of structural organization. These include the chemical, cellular, tissue, organ, organ system, and the organism level. Higher levels of organization are built from lower levels. Therefore, molecules combine to form cells, cells combine to form tissues, tissues combine to form organs, organs combine to form organ systems, and organ systems combine to form organisms.

Review Questions

The smallest independently functioning unit of an organism is a(n) ______.

1. cell

2. molecule
3. organ
4. tissue

A

A collection of similar tissues that performs a specific function is an ______.

1. organ
2. organelle
3. organism
4. organ system

A

The body system responsible for structural support and movement is the ______.

1. cardiovascular system
2. endocrine system
3. muscular system
4. skeletal system

D

CRITICAL THINKING QUESTIONS

Name the six levels of organization of the human body.

Chemical, cellular, tissue, organ, organ system, organism.

The female ovaries and the male testes are a part of which body system? Can these organs be members of more than one organ system? Why or why not?

The female ovaries and the male testes are parts of the reproductive system. But they also secrete hormones, as does the endocrine system, therefore ovaries and testes function within both the endocrine and reproductive systems.

Glossary

cell
: smallest independently functioning unit of all organisms; in animals, a cell contains cytoplasm, composed of fluid and organelles

organ
: functionally distinct structure composed of two or more types of tissues

organ system
: group of organs that work together to carry out a particular function

organism
: living being that has a cellular structure and that can independently perform all physiologic functions necessary for life

tissue
: group of similar or closely related cells that act together to perform a specific function

Functions of Human Life
By the end of this section, you will be able to:

- Explain the importance of organization to the function of the human organism
- Distinguish between metabolism, anabolism, and catabolism
- Provide at least two examples of human responsiveness and human movement
- Compare and contrast growth, differentiation, and reproduction

The different organ systems each have different functions and therefore unique roles to perform in physiology. These many functions can be summarized in terms of a few that we might consider definitive of human life: organization, metabolism, responsiveness, movement, development, and reproduction.

Organization

A human body consists of trillions of cells organized in a way that maintains distinct internal compartments. These compartments keep body cells separated from external environmental threats and keep the cells moist and nourished. They also separate internal body fluids from the countless microorganisms that grow on body surfaces,

including the lining of certain tracts, or passageways. The intestinal tract, for example, is home to even more bacteria cells than the total of all human cells in the body, yet these bacteria are outside the body and cannot be allowed to circulate freely inside the body.

Cells, for example, have a cell membrane (also referred to as the plasma membrane) that keeps the intracellular environment—the fluids and organelles—separate from the extracellular environment. Blood vessels keep blood inside a closed circulatory system, and nerves and muscles are wrapped in connective tissue sheaths that separate them from surrounding structures. In the chest and abdomen, a variety of internal membranes keep major organs such as the lungs, heart, and kidneys separate from others.

The body's largest organ system is the integumentary system, which includes the skin and its associated structures, such as hair and nails. The surface tissue of skin is a barrier that protects internal structures and fluids from potentially harmful microorganisms and other toxins.

Metabolism

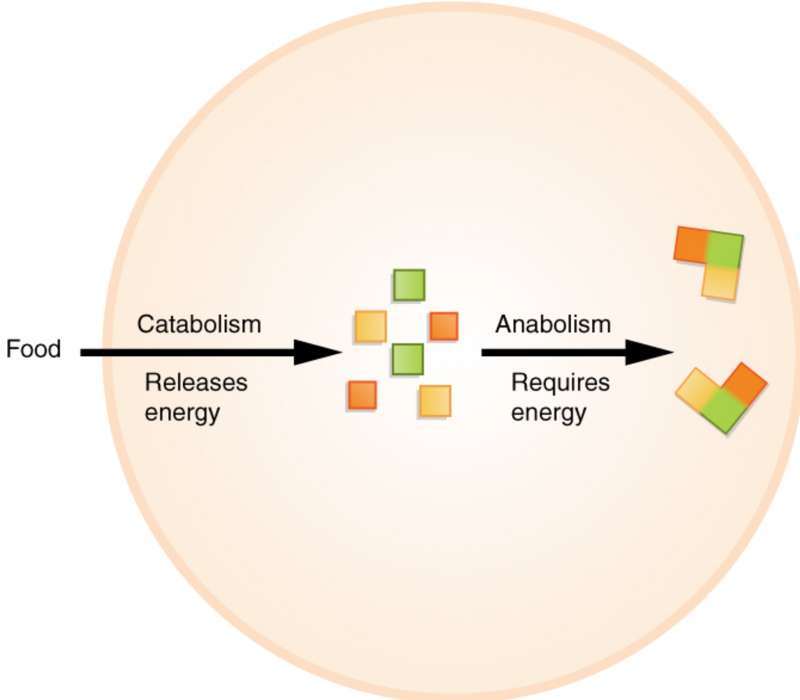
The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only

change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: **anabolism** and **catabolism**.

- **Anabolism** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat
- **Catabolism** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.

Taken together, these two processes are called metabolism. **Metabolism** is the sum of all anabolic and catabolic reactions that take place in the body ([link]). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.
Metabolism
Anabolic reactions are building reactions, and they consume energy. Catabolic reactions break materials down and release energy. Metabolism includes both

anabolic and catabolic reactions.



Every cell in your body makes use of a chemical compound, **adenosine triphosphate (ATP)**, to store and release energy. The cell stores energy in the synthesis (anabolism) of ATP, then moves the ATP molecules to the location where energy is needed to fuel cellular activities. Then the ATP is broken down (catabolism) and a controlled amount of energy is released, which is used by the cell to perform a particular job.

View this animation to learn more about metabolic processes. Which organs of the body likely carry out anabolic processes? What about catabolic processes?

Responsiveness

Responsiveness is the ability of an organism to adjust to changes in its internal and external environments. An example of responsiveness to external stimuli could include moving toward sources of food and water and away from perceived dangers. Changes in an organism’s internal environment, such as increased body temperature, can cause the responses of sweating and the dilation of blood vessels in the skin in order to decrease body temperature, as shown by the runners in [link].

Movement

Human movement includes not only actions at the joints of the body, but also the motion of individual organs and even individual cells. As you read these words, red and white blood cells are moving throughout your body, muscle cells are contracting and relaxing to maintain your posture and to focus your vision, and glands are secreting chemicals to regulate body functions. Your body is coordinating the action of entire muscle groups to enable you to move air into and out of your lungs, to push blood throughout your body, and to propel the food you have eaten through your digestive tract. Consciously, of course, you contract your skeletal muscles to move the bones of your skeleton to get from one place to another (as the runners are doing in [link]), and to carry out all of the activities of your daily life.

Marathon Runners

Runners demonstrate two characteristics of living humans—responsiveness and movement. Anatomic structures and physiological processes allow runners to coordinate the action of muscle groups and sweat in response to rising internal body temperature. (credit: Phil Roeder/flickr)

Development, growth and reproduction

Development is all of the changes the body goes through in life. Development includes the process of **differentiation**, in which unspecialized cells become specialized in structure and function to perform certain tasks in the body. Development also includes the processes of growth and repair, both of which involve cell differentiation.

Growth is the increase in body size. Humans, like all multicellular organisms, grow by increasing the number of existing cells, increasing the amount of non-cellular material around cells (such as mineral deposits in bone), and, within very narrow limits, increasing the size of existing cells.

Reproduction is the formation of a new organism from parent organisms. In humans, reproduction is carried out by the male and female reproductive systems. Because death will come to all complex organisms, without reproduction, the line of organisms would end.

Chapter Review

Most processes that occur in the human body are not consciously controlled. They occur continuously to build, maintain, and sustain life. These processes include: organization, in terms of the maintenance of essential body boundaries; metabolism, including energy transfer via anabolic and catabolic reactions; responsiveness; movement; and growth, differentiation, reproduction, and renewal.

Interactive Link Questions

View this animation to learn more about metabolic processes. What kind of catabolism occurs in the heart?

Fatty acid catabolism.

Review Questions

Metabolism can be defined as the _____.

1. adjustment by an organism to external or internal changes
2. process whereby all unspecialized cells become specialized to perform distinct functions
3. process whereby new cells are formed to replace worn-out cells
4. sum of all chemical reactions in an organism

D

Adenosine triphosphate (ATP) is an important molecule because it _____.

1. is the result of catabolism
2. release energy in uncontrolled bursts
3. stores energy for use by body cells
4. All of the above

C

Cancer cells can be characterized as “generic”

cells that perform no specialized body function. Thus cancer cells lack ______.

1. differentiation
2. reproduction
3. responsiveness
4. both reproduction and responsiveness

A

CRITICAL THINKING QUESTIONS

Explain why the smell of smoke when you are sitting at a campfire does not trigger alarm, but the smell of smoke in your residence hall does.

When you are sitting at a campfire, your sense of smell adapts to the smell of smoke. Only if that smell were to suddenly and dramatically intensify would you be likely to notice and respond. In contrast, the smell of even a trace of smoke would be new and highly unusual in your residence hall, and would be perceived as danger.

Identify three different ways that growth can occur in the human body.

Growth can occur by increasing the number of existing cells, increasing the size of existing cells, or increasing the amount of non-cellular material around cells.

Glossary

anabolism
: assembly of more complex molecules from simpler molecules

catabolism
: breaking down of more complex molecules into simpler molecules

development
: changes an organism goes through during its life

differentiation
: process by which unspecialized cells become specialized in structure and function

growth
: process of increasing in size

metabolism

sum of all of the body's chemical reactions

renewal
: process by which worn-out cells are replaced

reproduction
: process by which new organisms are generated

responsiveness
: ability of an organisms or a system to adjust to changes in conditions

Homeostasis

By the end of this section, you will be able to:

- Discuss the role of homeostasis in healthy functioning
- Contrast negative and positive feedback, giving one physiologic example of each mechanism

Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A **set point** is the physiological value around which the normal range fluctuates. A **normal range** is the restricted set of values that is optimally healthful and stable. For example, the set point for normal human body temperature is approximately 37°C (98.6°F) Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a normal range a few degrees above and below that point. Control centers in the brain and other parts of the body monitor and react to deviations from homeostasis using negative feedback. **Negative feedback** is a mechanism that reverses a deviation from the set point. Therefore, negative feedback maintains body parameters within their normal range. The maintenance of homeostasis by negative feedback goes on throughout the body at all times, and an understanding of negative feedback is thus fundamental to an understanding of human

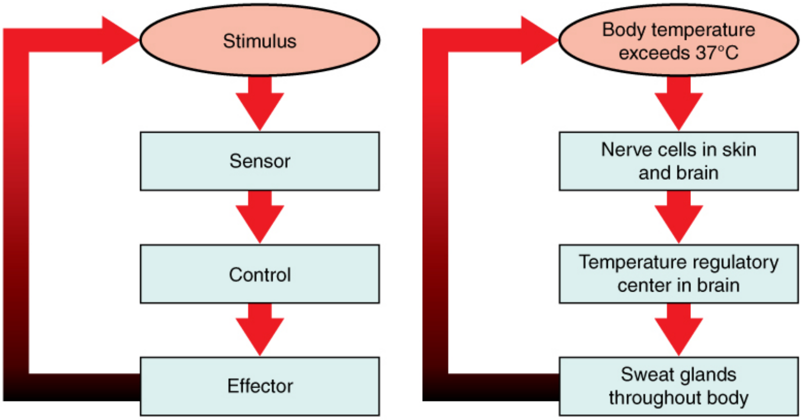
physiology.

Negative Feedback

A negative feedback system has three basic components ([link]**a**). A **sensor**, also referred to a receptor, is a component of a feedback system that monitors a physiological value. This value is reported to the control center. The **control center** is the component in a feedback system that compares the value to the normal range. If the value deviates too much from the set point, then the control center activates an effector. An **effector** is the component in a feedback system that causes a change to reverse the situation and return the value to the normal range.

Negative Feedback Loop

In a negative feedback loop, a stimulus—a deviation from a set point—is resisted through a physiological process that returns the body to homeostasis. (a) A negative feedback loop has four basic parts. (b) Body temperature is regulated by negative feedback.



(a) Negative feedback loop (b) Body temperature regulation

In order to set the system in motion, a stimulus must drive a physiological parameter beyond its normal range (that is, beyond homeostasis). This stimulus is "heard" by a specific sensor. For example, in the control of blood glucose, specific endocrine cells in the pancreas detect excess glucose (the stimulus) in the bloodstream. These pancreatic beta cells respond to the increased level of blood glucose by releasing the hormone insulin into the bloodstream. The insulin signals skeletal muscle fibers, fat cells (adipocytes), and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the bloodstream drops, the decrease in concentration—the actual negative feedback—is detected by pancreatic alpha cells, and insulin release stops. This prevents blood sugar levels from continuing to drop below the normal range.

Humans have a similar temperature regulation

feedback system that works by promoting either heat loss or heat gain ([link]**b**). When the brain's temperature regulation center receives data from the sensors indicating that the body's temperature exceeds its normal range, it stimulates a cluster of brain cells referred to as the "heat-loss center." This stimulation has three major effects:

- Blood vessels in the skin begin to dilate allowing more blood from the body core to flow to the surface of the skin allowing the heat to radiate into the environment.
- As blood flow to the skin increases, sweat glands are activated to increase their output. As the sweat evaporates from the skin surface into the surrounding air, it takes heat with it.
- The depth of respiration increases, and a person may breathe through an open mouth instead of through the nasal passageways. This further increases heat loss from the lungs.

In contrast, activation of the brain's heat-gain center by exposure to cold reduces blood flow to the skin, and blood returning from the limbs is diverted into a network of deep veins. This arrangement traps heat closer to the body core and restricts heat loss. If heat loss is severe, the brain triggers an increase in random signals to skeletal muscles, causing them to contract and producing shivering. The muscle contractions of shivering release heat while using up ATP. The brain triggers the thyroid gland in the

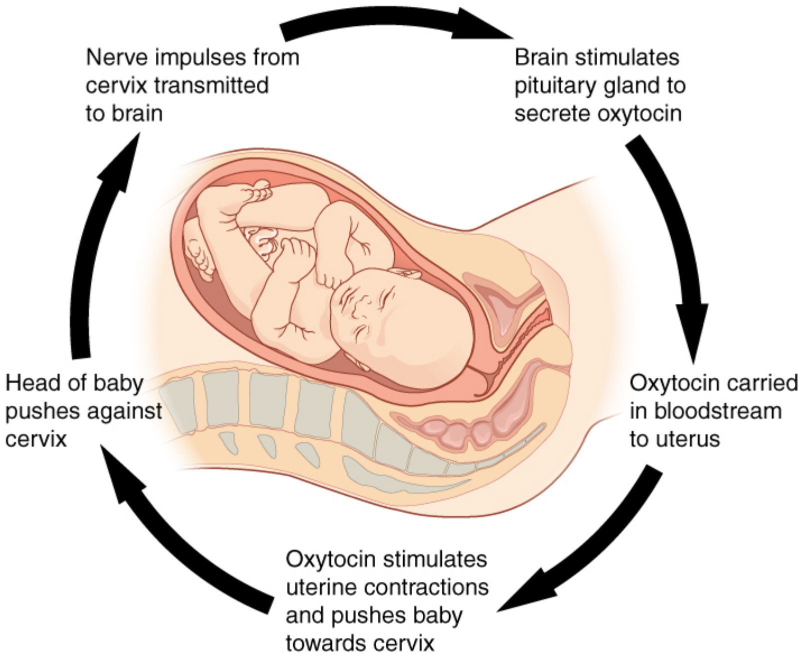
endocrine system to release thyroid hormone, which increases metabolic activity and heat production in cells throughout the body. The brain also signals the adrenal glands to release epinephrine (adrenaline), a hormone that causes the breakdown of glycogen into glucose, which can be used as an energy source. The breakdown of glycogen into glucose also results in increased metabolism and heat production.

Water concentration in the body is critical for proper functioning. A person’s body retains very tight control on water levels without conscious control by the person. Watch this video to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

Positive Feedback

Positive feedback intensifies a change in the body's physiological condition rather than reversing it. A deviation from the normal range results in more change, and the system moves farther away from the normal range. Positive feedback in the body is normal only when there is a definite end point. Childbirth and the body's response to blood loss are two examples of positive feedback loops that are normal but are activated only when needed.

Childbirth at full term is an example of a situation in which the maintenance of the existing body state is not desired. Enormous changes in the mother's body are required to expel the baby at the end of pregnancy. And the events of childbirth, once begun, must progress rapidly to a conclusion or the life of the mother and the baby are at risk. The extreme muscular work of labor and delivery are the result of a positive feedback system ([link]).
Positive Feedback Loop
Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.



The first contractions of labor (the stimulus) push the baby toward the cervix (the lowest part of the uterus). The cervix contains stretch-sensitive nerve cells that monitor the degree of stretching (the sensors). These nerve cells send messages to the brain, which in turn causes the pituitary gland at the base of the brain to release the hormone oxytocin into the bloodstream. Oxytocin causes stronger contractions of the smooth muscles in of the uterus (the effectors), pushing the baby further down the birth canal. This causes even greater stretching of the cervix. The cycle of stretching, oxytocin release, and increasingly more forceful contractions stops only when the baby is born. At this point, the stretching of the cervix halts, stopping the release of oxytocin.

A second example of positive feedback centers on reversing extreme damage to the body. Following a penetrating wound, the most immediate threat is excessive blood loss. Less blood circulating means reduced blood pressure and reduced perfusion (penetration of blood) to the brain and other vital organs. If perfusion is severely reduced, vital organs will shut down and the person will die. The body responds to this potential catastrophe by releasing substances in the injured blood vessel wall that begin the process of blood clotting. As each step of clotting occurs, it stimulates the release of more clotting substances. This accelerates the processes of clotting and sealing off the damaged area. Clotting is contained in a local area based on the tightly controlled availability of clotting proteins. This is an adaptive, life-saving cascade of events.

Chapter Review

Homeostasis is the activity of cells throughout the body to maintain the physiological state within a narrow range that is compatible with life. Homeostasis is regulated by negative feedback loops and, much less frequently, by positive feedback loops. Both have the same components of a stimulus, sensor, control center, and effector; however, negative feedback loops work to prevent an excessive response to the stimulus, whereas positive feedback loops intensify the response until

an end point is reached.

Interactive Link Questions

Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this video to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

The kidneys.

Review Questions

After you eat lunch, nerve cells in your stomach respond to the distension (the stimulus) resulting from the food. They relay this information to ______.

1. a control center
2. a set point
3. effectors

4. sensors

A

Stimulation of the heat-loss center causes _____.

1. blood vessels in the skin to constrict
2. breathing to become slow and shallow
3. sweat glands to increase their output
4. All of the above

C

Which of the following is an example of a normal physiologic process that uses a positive feedback loop?

1. blood pressure regulation
2. childbirth
3. regulation of fluid balance
4. temperature regulation

B

Critical Thinking Questions

Identify the four components of a negative feedback loop and explain what would happen if secretion of a body chemical controlled by a negative feedback system became too great.

The four components of a negative feedback loop are: stimulus, sensor, control center, and effector. If too great a quantity of the chemical were excreted, sensors would activate a control center, which would in turn activate an effector. In this case, the effector (the secreting cells) would be adjusted downward.

What regulatory processes would your body use if you were trapped by a blizzard in an unheated, uninsulated cabin in the woods?

Any prolonged exposure to extreme cold would activate the brain's heat-gain center. This would reduce blood flow to your skin, and shunt blood returning from your limbs away from the digits and into a network of deep veins. Your brain's heat-gain center would also increase your muscle contraction, causing you to shiver. This increases the energy consumption of skeletal

muscle and generates more heat. Your body would also produce thyroid hormone and epinephrine, chemicals that promote increased metabolism and heat production.

Glossary

control center
: compares values to their normal range; deviations cause the activation of an effector

effector
: organ that can cause a change in a value

negative feedback
: homeostatic mechanism that tends to stabilize an upset in the body's physiological condition by preventing an excessive response to a stimulus, typically as the stimulus is removed

normal range
: range of values around the set point that do not cause a reaction by the control center

positive feedback
: mechanism that intensifies a change in the body's physiological condition in response to a stimulus

sensor
: (also, receptor) reports a monitored

physiological value to the control center

set point
: ideal value for a physiological parameter; the level or small range within which a physiological parameter such as blood pressure is stable and optimally healthful, that is, within its parameters of homeostasis

Medical Imaging

By the end of this section, you will be able to:

- Discuss the uses and drawbacks of X-ray imaging
- Identify four modern medical imaging techniques and how they are used

For thousands of years, fear of the dead and legal sanctions limited the ability of anatomists and physicians to study the internal structures of the human body. An inability to control bleeding, infection, and pain made surgeries infrequent, and those that were performed—such as wound suturing, amputations, tooth and tumor removals, skull drilling, and cesarean births—did not greatly advance knowledge about internal anatomy. Theories about the function of the body and about disease were therefore largely based on external observations and imagination. During the fourteenth and fifteenth centuries, however, the detailed anatomical drawings of Italian artist and anatomist Leonardo da Vinci and Flemish anatomist Andreas Vesalius were published, and interest in human anatomy began to increase. Medical schools began to teach anatomy using human dissection; although some resorted to grave robbing to obtain corpses. Laws were eventually passed that enabled students to dissect the corpses of criminals and those who donated their bodies for research. Still, it was not until the late nineteenth century that medical

researchers discovered non-surgical methods to look inside the living body.

X-Rays

German physicist Wilhelm Röntgen (1845–1923) was experimenting with electrical current when he discovered that a mysterious and invisible “ray” would pass through his flesh but leave an outline of his bones on a screen coated with a metal compound. In 1895, Röntgen made the first durable record of the internal parts of a living human: an “X-ray” image (as it came to be called) of his wife’s hand. Scientists around the world quickly began their own experiments with X-rays, and by 1900, X-rays were widely used to detect a variety of injuries and diseases. In 1901, Röntgen was awarded the first Nobel Prize for physics for his work in this field.

The **X-ray** is a form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids and ionizing gases. As they are used in medicine, X-rays are emitted from an X-ray machine and directed toward a specially treated metallic plate placed behind the patient’s body. The beam of radiation results in darkening of the X-ray plate. X-rays are slightly impeded by soft tissues, which show up as gray on the X-ray plate, whereas hard tissues, such as bone, largely block the rays,

producing a light-toned “shadow.” Thus, X-rays are best used to visualize hard body structures such as teeth and bones ([link]). Like many forms of high energy radiation, however, X-rays are capable of damaging cells and initiating changes that can lead to cancer. This danger of excessive exposure to X-rays was not fully appreciated for many years after their widespread use.

X-Ray of a Hand

High energy electromagnetic radiation allows the internal structures of the body, such as bones, to be seen in X-rays like these. (credit: Trace Meek/flickr)

Refinements and enhancements of X-ray techniques have continued throughout the twentieth and twenty-first centuries. Although often supplanted by more sophisticated imaging techniques, the X-ray remains a “workhorse” in medical imaging, especially for viewing fractures and for dentistry. The disadvantage of irradiation to the patient and the operator is now attenuated by proper shielding and by limiting exposure.

Modern Medical Imaging

X-rays can depict a two-dimensional image of a body region, and only from a single angle. In contrast, more recent medical imaging technologies produce data that is integrated and analyzed by computers to produce three-dimensional images or images that reveal aspects of body functioning.

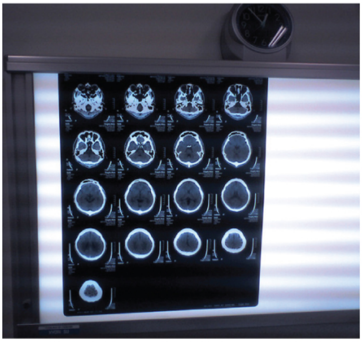
Computed Tomography

Tomography refers to imaging by sections. **Computed tomography (CT)** is a noninvasive imaging technique that uses computers to analyze several cross-sectional X-rays in order to reveal minute details about structures in the body ([link]**a**). The technique was invented in the 1970s and is based on the principle that, as X-rays pass through the body, they are absorbed or reflected at

different levels. In the technique, a patient lies on a motorized platform while a computerized axial tomography (CAT) scanner rotates 360 degrees around the patient, taking X-ray images. A computer combines these images into a two-dimensional view of the scanned area, or “slice.”

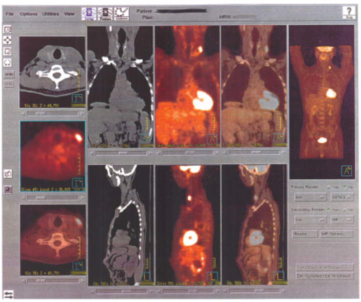
Medical Imaging Techniques

(a) The results of a CT scan of the head are shown as successive transverse sections. (b) An MRI machine generates a magnetic field around a patient. (c) PET scans use radiopharmaceuticals to create images of active blood flow and physiologic activity of the organ or organs being targeted. (d) Ultrasound technology is used to monitor pregnancies because it is the least invasive of imaging techniques and uses no electromagnetic radiation. (credit a: Akira Ohgaki/flickr; credit b: “Digital Cate”/flickr; credit c: “Raziel”/Wikimedia Commons; credit d: “Isis”/Wikimedia Commons)

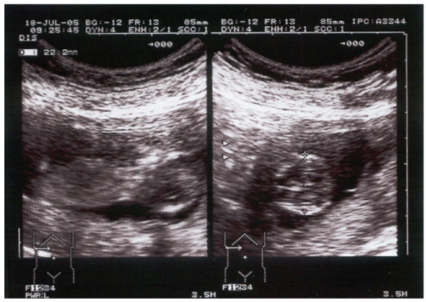


(a)

(b)



(c)



(d)

Since 1970, the development of more powerful computers and more sophisticated software has made CT scanning routine for many types of diagnostic evaluations. It is especially useful for soft tissue scanning, such as of the brain and the thoracic and abdominal viscera. Its level of detail is so precise that it can allow physicians to measure the size of a mass down to a millimeter. The main disadvantage of CT scanning is that it exposes patients to a dose of radiation many times higher than that of X-rays. In fact, children who undergo CT scans are at increased risk of developing cancer, as are adults who have multiple CT scans.

A CT or CAT scan relies on a circling scanner that revolves around the patient’s body. Watch this video to learn more about CT and CAT scans. What type of radiation does a CT scanner use?

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique based on a phenomenon of nuclear physics discovered in the 1930s, in which matter exposed to magnetic fields and radio waves was found to emit radio signals. In 1970, a physician and researcher named Raymond Damadian noticed that malignant (cancerous) tissue gave off different signals than normal body tissue. He applied for a patent for the first MRI scanning device, which was in use clinically by the early 1980s. The early MRI scanners were crude, but advances in digital computing and electronics led to their advancement over any other technique for precise imaging, especially to discover tumors. MRI

also has the major advantage of not exposing patients to radiation.

Drawbacks of MRI scans include their much higher cost, and patient discomfort with the procedure. The MRI scanner subjects the patient to such powerful electromagnets that the scan room must be shielded. The patient must be enclosed in a metal tube-like device for the duration of the scan (see [link]**b**), sometimes as long as thirty minutes, which can be uncomfortable and impractical for ill patients. The device is also so noisy that, even with earplugs, patients can become anxious or even fearful. These problems have been overcome somewhat with the development of "open" MRI scanning, which does not require the patient to be entirely enclosed in the metal tube. Patients with iron-containing metallic implants (internal sutures, some prosthetic devices, and so on) cannot undergo MRI scanning because it can dislodge these implants.

Functional MRIs (fMRIs), which detect the concentration of blood flow in certain parts of the body, are increasingly being used to study the activity in parts of the brain during various body activities. This has helped scientists learn more about the locations of different brain functions and more about brain abnormalities and diseases.

A patient undergoing an MRI is surrounded by a tube-shaped scanner. Watch this video to learn more about MRIs. What is the function of magnets in an MRI?

Positron Emission Tomography

Positron emission tomography (PET) is a medical imaging technique involving the use of so-called radiopharmaceuticals, substances that emit radiation that is short-lived and therefore relatively safe to administer to the body. Although the first PET scanner was introduced in 1961, it took 15 more years before radiopharmaceuticals were combined with the technique and revolutionized its potential. The main advantage is that PET (see [link]**c**) can illustrate physiologic activity—including nutrient metabolism and blood flow—of the organ or organs being targeted, whereas CT and MRI scans can only show static images. PET is widely used to diagnose a multitude of conditions, such as heart disease, the spread of cancer, certain

forms of infection, brain abnormalities, bone disease, and thyroid disease.

PET relies on radioactive substances administered several minutes before the scan. Watch this video to learn more about PET. How is PET used in chemotherapy?

Ultrasonography

Ultrasonography is an imaging technique that uses the transmission of high-frequency sound waves into the body to generate an echo signal that is converted by a computer into a real-time image of anatomy and physiology (see [link]**d**). Ultrasonography is the least invasive of all imaging techniques, and it is therefore used more freely in sensitive situations such as pregnancy. The technology was first developed in the 1940s and

1950s. Ultrasonography is used to study heart function, blood flow in the neck or extremities, certain conditions such as gallbladder disease, and fetal growth and development. The main disadvantages of ultrasonography are that the image quality is heavily operator-dependent and that it is unable to penetrate bone and gas.

Chapter Review

Detailed anatomical drawings of the human body first became available in the fifteenth and sixteenth centuries; however, it was not until the end of the nineteenth century, and the discovery of X-rays, that anatomists and physicians discovered non-surgical methods to look inside a living body. Since then, many other techniques, including CT scans, MRI scans, PET scans, and ultrasonography, have been developed, providing more accurate and detailed views of the form and function of the human body.

Interactive Link Questions

A CT or CAT scan relies on a circling scanner that revolves around the patient's body. Watch this video to learn more about CT and CAT scans. What type of radiation does a CT scanner

use?

X-rays.

A patient undergoing an MRI is surrounded by a tube-shaped scanner. Watch this video to learn more about MRIs. What is the function of magnets in an MRI?

The magnets induce tissue to emit radio signals that can show differences between different types of tissue.

PET relies on radioactive substances administered several minutes before the scan. Watch this video to learn more about PET. How is PET used in chemotherapy?

PET scans can indicate how patients are responding to chemotherapy.

Review Questions

In 1901, Wilhelm Röntgen was the first person

to win the Nobel Prize for physics. For what discovery did he win?

1. nuclear physics
2. radiopharmaceuticals
3. the link between radiation and cancer
4. X-rays

D

Which of the following imaging techniques would be best to use to study the uptake of nutrients by rapidly multiplying cancer cells?

1. CT
2. MRI
3. PET
4. ultrasonography

C

Which of the following imaging studies can be used most safely during pregnancy?

1. CT scans
2. PET scans
3. ultrasounds
4. X-rays

C

What are two major disadvantages of MRI scans?

1. release of radiation and poor quality images
2. high cost and the need for shielding from the magnetic signals
3. can only view metabolically active tissues and inadequate availability of equipment
4. release of radiation and the need for a patient to be confined to metal tube for up to 30 minutes

B

Critical Thinking Questions

Which medical imaging technique is most dangerous to use repeatedly, and why?

CT scanning subjects patients to much higher levels of radiation than X-rays, and should not be performed repeatedly.

Explain why ultrasound imaging is the technique of choice for studying fetal growth and development.

Ultrasonography does not expose a mother or fetus to radiation, to radiopharmaceuticals, or to magnetic fields. At this time, there are no known medical risks of ultrasonography.

Glossary

computed tomography (CT)
: medical imaging technique in which a computer-enhanced cross-sectional X-ray image is obtained

magnetic resonance imaging (MRI)
: medical imaging technique in which a device generates a magnetic field to obtain detailed sectional images of the internal structures of the body

positron emission tomography (PET)
: medical imaging technique in which radiopharmaceuticals are traced to reveal metabolic and physiological functions in tissues

ultrasonography
: application of ultrasonic waves to visualize

subcutaneous body structures such as tendons and organs

X-ray
: form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids and ionizing gases; used in medicine as a diagnostic aid to visualize body structures such as bones

Introduction
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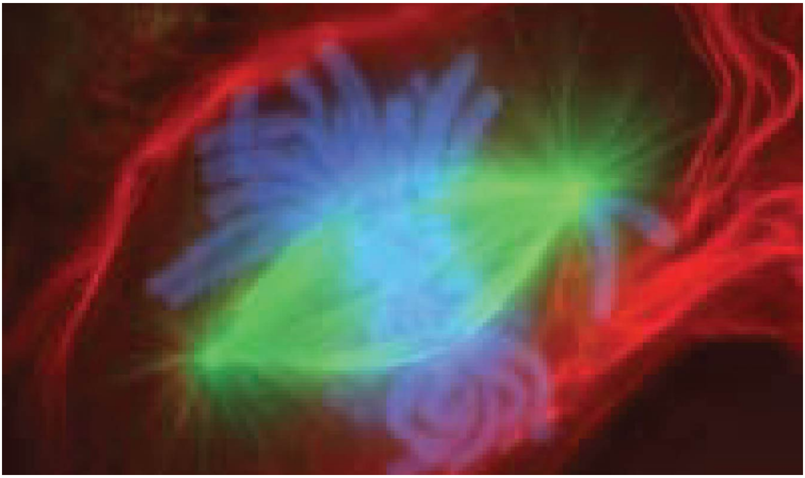
Fluorescence-stained Cell Undergoing Mitosis
A lung cell from a newt, commonly studied for its similarity to human lung cells, is stained with fluorescent dyes. The green stain reveals mitotic spindles, red is the cell membrane and part of the cytoplasm, and the structures that appear light blue are chromosomes. This cell is in anaphase of mitosis. (credit: “Mortadelo2005”/Wikimedia Commons)



Chapter Objectives

After studying this chapter, you will be able to:

- Describe the structure and function of the cell membrane, including its regulation of materials into and out of the cell

- Describe the functions of the various cytoplasmic organelles
- Explain the structure and contents of the nucleus, as well as the process of DNA replication
- Explain the process by which a cell builds proteins using the DNA code
- List the stages of the cell cycle in order, including the steps of cell division in somatic cells
- Discuss how a cell differentiates and becomes more specialized
- List the morphological and physiological characteristics of some representative cell types in the human body

You developed from a single fertilized egg cell into the complex organism containing trillions of cells that you see when you look in a mirror. During this developmental process, early, undifferentiated cells differentiate and become specialized in their structure and function. These different cell types form specialized tissues that work in concert to perform all of the functions necessary for the living organism. Cellular and developmental biologists study how the continued division of a single cell leads to such complexity and differentiation.

Consider the difference between a structural cell in

the skin and a nerve cell. A structural skin cell may be shaped like a flat plate (squamous) and live only for a short time before it is shed and replaced. Packed tightly into rows and sheets, the squamous skin cells provide a protective barrier for the cells and tissues that lie beneath. A nerve cell, on the other hand, may be shaped something like a star, sending out long processes up to a meter in length and may live for the entire lifetime of the organism. With their long winding appendages, nerve cells can communicate with one another and with other types of body cells and send rapid signals that inform the organism about its environment and allow it to interact with that environment. These differences illustrate one very important theme that is consistent at all organizational levels of biology: the form of a structure is optimally suited to perform particular functions assigned to that structure. Keep this theme in mind as you tour the inside of a cell and are introduced to the various types of cells in the body.

A primary responsibility of each cell is to contribute to homeostasis. Homeostasis is a term used in biology that refers to a dynamic state of balance within parameters that are compatible with life. For example, living cells require a water-based environment to survive in, and there are various physical (anatomical) and physiological mechanisms that keep all of the trillions of living cells in the human body moist. This is one aspect of

homeostasis. When a particular parameter, such as blood pressure or blood oxygen content, moves far enough *out* of homeostasis (generally becoming too high or too low), illness or disease—and sometimes death—inevitably results.

The concept of a cell started with microscopic observations of dead cork tissue by scientist Robert Hooke in 1665. Without realizing their function or importance, Hook coined the term “cell” based on the resemblance of the small subdivisions in the cork to the rooms that monks inhabited, called cells. About ten years later, Antonie van Leeuwenhoek became the first person to observe living and moving cells under a microscope. In the century that followed, the theory that cells represented the basic unit of life would develop. These tiny fluid-filled sacs house components responsible for the thousands of biochemical reactions necessary for an organism to grow and survive. In this chapter, you will learn about the major components and functions of a prototypical, generalized cell and discover some of the different types of cells in the human body.

The Cell Membrane
By the end of this section, you will be able to:

- Describe the molecular components that make up the cell membrane
- Explain the major features and properties of the cell membrane
- Differentiate between materials that can and cannot diffuse through the lipid bilayer
- Compare and contrast different types of passive transport with active transport, providing examples of each

Despite differences in structure and function, all living cells in multicellular organisms have a surrounding cell membrane. As the outer layer of your skin separates your body from its environment, the cell membrane (also known as the plasma membrane) separates the inner contents of a cell from its exterior environment. This cell membrane provides a protective barrier around the cell and regulates which materials can pass in or out.

Structure and Composition of the Cell Membrane

The **cell membrane** is an extremely pliable structure composed primarily of back-to-back phospholipids (a “bilayer”). Cholesterol is also

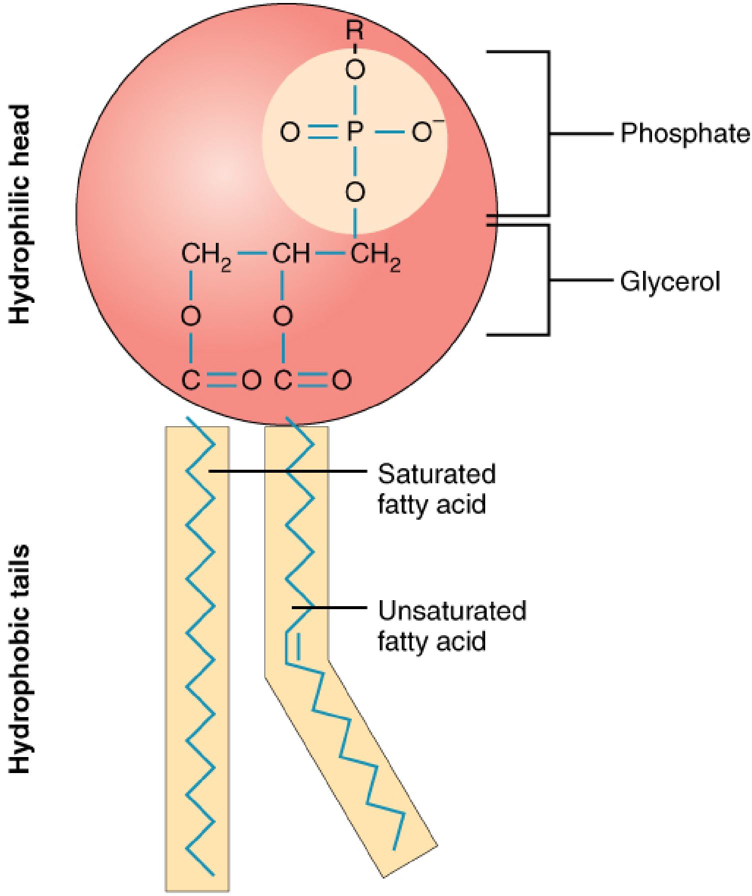
present, which contributes to the fluidity of the membrane, and there are various proteins embedded within the membrane that have a variety of functions.

A single phospholipid molecule has a phosphate group on one end, called the “head,” and two side-by-side chains of fatty acids that make up the lipid tails ([link]). The phosphate group is negatively charged, making the head polar and hydrophilic—or “water loving.” A **hydrophilic** molecule (or region of a molecule) is one that is attracted to water. The phosphate heads are thus attracted to the water molecules of both the extracellular and intracellular environments. The lipid tails, on the other hand, are uncharged, or nonpolar, and are hydrophobic—or “water fearing.” A **hydrophobic** molecule (or region of a molecule) repels and is repelled by water. Some lipid tails consist of saturated fatty acids and some contain unsaturated fatty acids. This combination adds to the fluidity of the tails that are constantly in motion. Phospholipids are thus amphipathic molecules. An **amphipathic** molecule is one that contains both a hydrophilic and a hydrophobic region. In fact, soap works to remove oil and grease stains because it has amphipathic properties. The hydrophilic portion can dissolve in water while the hydrophobic portion can trap grease in micelles that then can be washed away.

Phospholipid Structure

A phospholipid molecule consists of a polar

phosphate “head,” which is hydrophilic and a non-polar lipid “tail,” which is hydrophobic. Unsaturated fatty acids result in kinks in the hydrophobic tails.

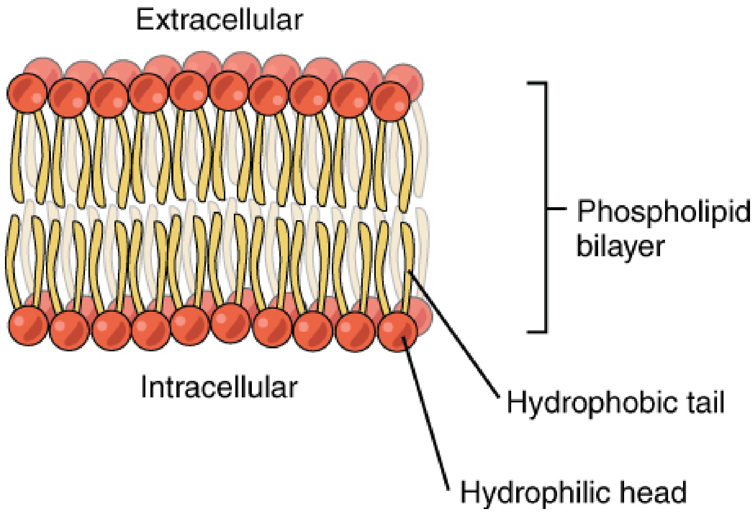


The cell membrane consists of two adjacent layers of phospholipids. The lipid tails of one layer face the lipid tails of the other layer, meeting at the interface of the two layers. The phospholipid heads face outward, one layer exposed to the interior of the cell and one layer exposed to the exterior ([link]). Because the phosphate groups are polar and

hydrophilic, they are attracted to water in the intracellular fluid. **Intracellular fluid (ICF)** is the fluid interior of the cell. The phosphate groups are also attracted to the extracellular fluid. **Extracellular fluid (ECF)** is the fluid environment outside the enclosure of the cell membrane. **Interstitial fluid (IF)** is the term given to extracellular fluid not contained within blood vessels. Because the lipid tails are hydrophobic, they meet in the inner region of the membrane, excluding watery intracellular and extracellular fluid from this space. The cell membrane has many proteins, as well as other lipids (such as cholesterol), that are associated with the phospholipid bilayer. An important feature of the membrane is that it remains fluid; the lipids and proteins in the cell membrane are not rigidly locked in place.

Phospolipid Bilayer

The phospholipid bilayer consists of two adjacent sheets of phospholipids, arranged tail to tail. The hydrophobic tails associate with one another, forming the interior of the membrane. The polar heads contact the fluid inside and outside of the cell.



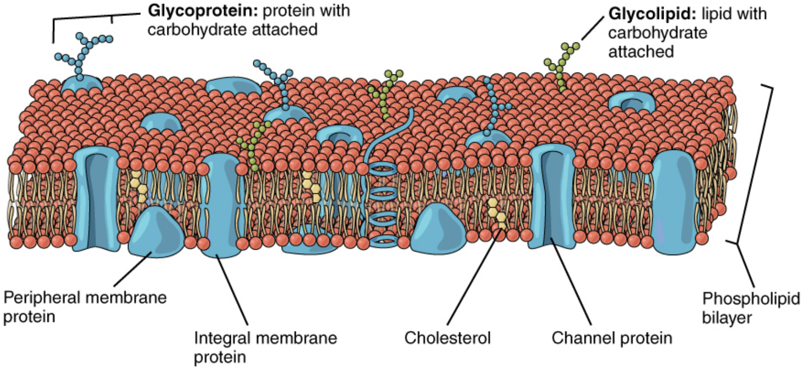
Membrane Proteins

The lipid bilayer forms the basis of the cell membrane, but it is peppered throughout with various proteins. Two different types of proteins that are commonly associated with the cell membrane are the integral proteins and peripheral protein ([link]). As its name suggests, an **integral protein** is a protein that is embedded in the membrane. A **channel protein** is an example of an integral protein that selectively allows particular materials, such as certain ions, to pass into or out of the cell.

Cell Membrane

The cell membrane of the cell is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol,

some with carbohydrate groups attached.



Another important group of integral proteins are cell recognition proteins, which serve to mark a cell's identity so that it can be recognized by other cells. A **receptor** is a type of recognition protein that can selectively bind a specific molecule outside the cell, and this binding induces a chemical reaction within the cell. A **ligand** is the specific molecule that binds to and activates a receptor. Some integral proteins serve dual roles as both a receptor and an ion channel. One example of a receptor-ligand interaction is the receptors on nerve cells that bind neurotransmitters, such as dopamine. When a dopamine molecule binds to a dopamine receptor protein, a channel within the transmembrane protein opens to allow certain ions to flow into the cell.

Some integral membrane proteins are glycoproteins. A **glycoprotein** is a protein that has carbohydrate molecules attached, which extend into the extracellular matrix. The attached carbohydrate tags

on glycoproteins aid in cell recognition. The carbohydrates that extend from membrane proteins and even from some membrane lipids collectively form the glycocalyx. The **glycocalyx** is a fuzzy-appearing coating around the cell formed from glycoproteins and other carbohydrates attached to the cell membrane. The glycocalyx can have various roles. For example, it may have molecules that allow the cell to bind to another cell, it may contain receptors for hormones, or it might have enzymes to break down nutrients. The glycocalyces found in a person's body are products of that person's genetic makeup. They give each of the individual's trillions of cells the "identity" of belonging in the person's body. This identity is the primary way that a person's immune defense cells "know" not to attack the person's own body cells, but it also is the reason organs donated by another person might be rejected.

Peripheral proteins are typically found on the inner or outer surface of the lipid bilayer but can also be attached to the internal or external surface of an integral protein. These proteins typically perform a specific function for the cell. Some peripheral proteins on the surface of intestinal cells, for example, act as digestive enzymes to break down nutrients to sizes that can pass through the cells and into the bloodstream.

Transport across the Cell Membrane

One of the great wonders of the cell membrane is its ability to regulate the concentration of substances inside the cell. These substances include ions such as Ca^{++}, Na^{+}, K^{+}, and Cl^{-}; nutrients including sugars, fatty acids, and amino acids; and waste products, particularly carbon dioxide (CO_2), which must leave the cell.

The membrane's lipid bilayer structure provides the first level of control. The phospholipids are tightly packed together, and the membrane has a hydrophobic interior. This structure causes the membrane to be selectively permeable. A membrane that has **selective permeability** allows only substances meeting certain criteria to pass through it unaided. In the case of the cell membrane, only relatively small, nonpolar materials can move through the lipid bilayer (remember, the lipid tails of the membrane are nonpolar). Some examples of these are other lipids, oxygen and carbon dioxide gases, and alcohol. However, water-soluble materials—like glucose, amino acids, and electrolytes—need some assistance to cross the membrane because they are repelled by the hydrophobic tails of the phospholipid bilayer. All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not energy is required. **Passive transport** is the movement of

substances across the membrane without the expenditure of cellular energy. In contrast, **active transport** is the movement of substances across the membrane using energy from adenosine triphosphate (ATP).

Passive Transport

In order to understand *how* substances move passively across a cell membrane, it is necessary to understand concentration gradients and diffusion. A **concentration gradient** is the difference in concentration of a substance across a space. Molecules (or ions) will spread/diffuse from where they are more concentrated to where they are less concentrated until they are equally distributed in that space. (When molecules move in this way, they are said to move *down* their concentration gradient.) **Diffusion** is the movement of particles from an area of higher concentration to an area of lower concentration. A couple of common examples will help to illustrate this concept. Imagine being inside a closed bathroom. If a bottle of perfume were sprayed, the scent molecules would naturally diffuse from the spot where they left the bottle to all corners of the bathroom, and this diffusion would go on until no more concentration gradient remains. Another example is a spoonful of sugar placed in a cup of tea. Eventually the sugar will diffuse throughout the tea until no concentration gradient remains. In both cases, if the room is warmer or the

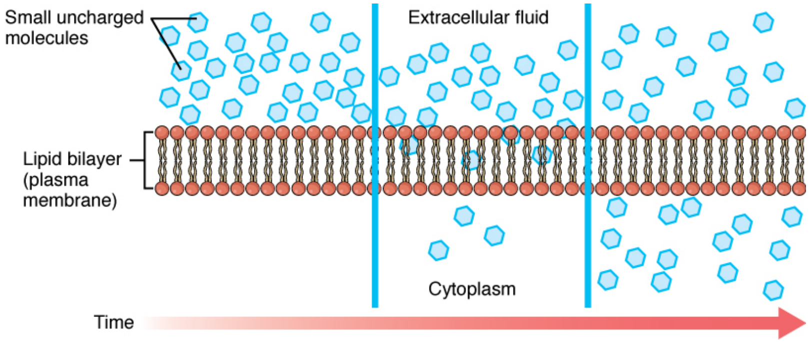
tea hotter, diffusion occurs even faster as the molecules are bumping into each other and spreading out faster than at cooler temperatures. Having an internal body temperature around 98.6° F thus also aids in diffusion of particles within the body.

Visit this link to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?

Whenever a substance exists in greater concentration on one side of a semipermeable membrane, such as the cell membranes, any substance that can move down its concentration gradient across the membrane will do so. Consider substances that can easily diffuse through the lipid bilayer of the cell membrane, such as the gases

oxygen (O_2) and CO_2. O_2 generally diffuses into cells because it is more concentrated outside of them, and CO_2 typically diffuses out of cells because it is more concentrated inside of them. Neither of these examples requires any energy on the part of the cell, and therefore they use passive transport to move across the membrane.

Before moving on, you need to review the gases that can diffuse across a cell membrane. Because cells rapidly use up oxygen during metabolism, there is typically a lower concentration of O_2 inside the cell than outside. As a result, oxygen will diffuse from the interstitial fluid directly through the lipid bilayer of the membrane and into the cytoplasm within the cell. On the other hand, because cells produce CO_2 as a byproduct of metabolism, CO_2 concentrations rise within the cytoplasm; therefore, CO_2 will move from the cell through the lipid bilayer and into the interstitial fluid, where its concentration is lower. This mechanism of molecules moving across a cell membrane from the side where they are more concentrated to the side where they are less concentrated is a form of passive transport called simple diffusion ([link]).
Simple Diffusion across the Cell (Plasma) Membrane
The structure of the lipid bilayer allows small, uncharged substances such as oxygen and carbon dioxide, and hydrophobic molecules such as lipids, to pass through the cell membrane, down their concentration gradient, by simple diffusion.

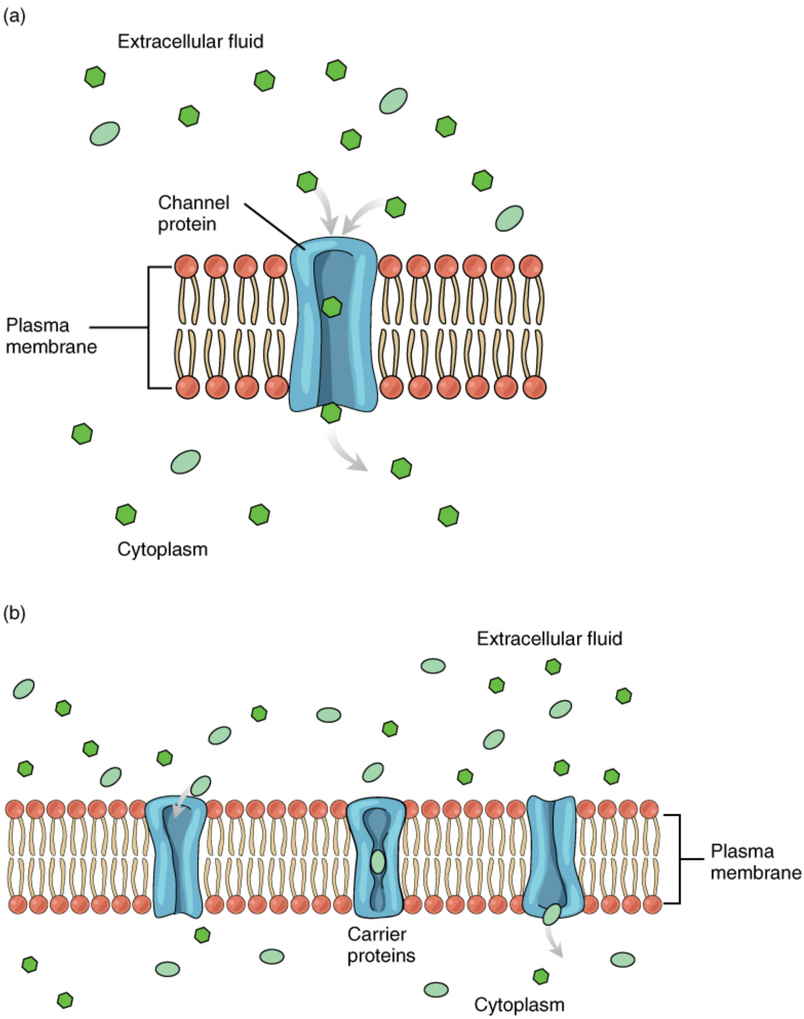


Large polar or ionic molecules, which are hydrophilic, cannot easily cross the phospholipid bilayer. Very small polar molecules, such as water, can cross via simple diffusion due to their small size. Charged atoms or molecules of any size cannot cross the cell membrane via simple diffusion as the charges are repelled by the hydrophobic tails in the interior of the phospholipid bilayer. Solutes dissolved in water on either side of the cell membrane will tend to diffuse down their concentration gradients, but because most substances cannot pass freely through the lipid bilayer of the cell membrane, their movement is restricted to protein channels and specialized transport mechanisms in the membrane. **Facilitated diffusion** is the diffusion process used for those substances that cannot cross the lipid bilayer due to their size, charge, and/or polarity ([link]). A common example of facilitated diffusion is the movement of glucose into the cell, where it is used to make ATP. Although glucose can be more concentrated outside of a cell, it cannot cross the lipid bilayer via simple diffusion because it is both

large and polar. To resolve this, a specialized carrier protein called the glucose transporter will transfer glucose molecules into the cell to facilitate its inward diffusion.

Facilitated Diffusion

(a) Facilitated diffusion of substances crossing the cell (plasma) membrane takes place with the help of proteins such as channel proteins and carrier proteins. Channel proteins are less selective than carrier proteins, and usually mildly discriminate between their cargo based on size and charge. (b) Carrier proteins are more selective, often only allowing one particular type of molecule to cross.



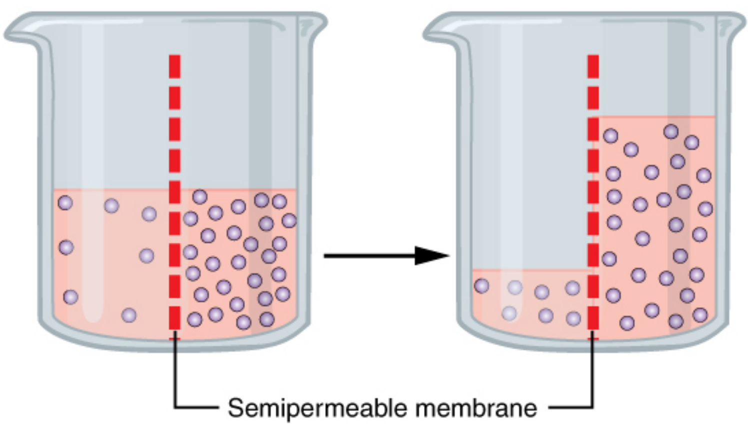
As an example, even though sodium ions ($Na+$) are highly concentrated outside of cells, these electrolytes are charged and cannot pass through the nonpolar lipid bilayer of the membrane. Their diffusion is facilitated by membrane proteins that form sodium channels (or "pores"), so that $Na+$ ions can move down their concentration gradient from outside the cells to inside the cells. There are many

other solutes that must undergo facilitated diffusion to move into a cell, such as amino acids, or to move out of a cell, such as wastes. Because facilitated diffusion is a passive process, it does not require energy expenditure by the cell.

Water also can move freely across the cell membrane of all cells, either through protein channels or by slipping between the lipid tails of the membrane itself. **Osmosis** is the diffusion of water through a semipermeable membrane ([link]).

Osmosis

Osmosis is the diffusion of water through a semipermeable membrane down its concentration gradient. If a membrane is permeable to water, though not to a solute, water will equalize its own concentration by diffusing to the side of lower water concentration (and thus the side of higher solute concentration). In the beaker on the left, the solution on the right side of the membrane is hypertonic.

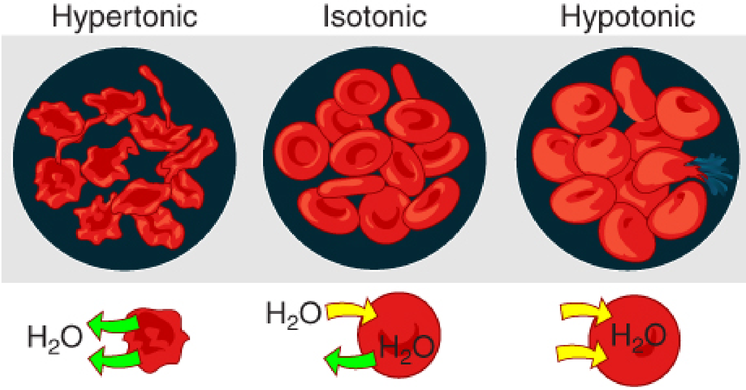


The movement of water molecules is not itself regulated by cells, so it is important that cells are exposed to an environment in which the concentration of solutes outside of the cells (in the extracellular fluid) is equal to the concentration of solutes inside the cells (in the cytoplasm). Two solutions that have the same concentration of solutes are said to be **isotonic** (equal tension). When cells and their extracellular environments are isotonic, the concentration of water molecules is the same outside and inside the cells, and the cells maintain their normal shape (and function).

Osmosis occurs when there is an imbalance of solutes outside of a cell versus inside the cell. A solution that has a higher concentration of solutes than another solution is said to be **hypertonic**, and water molecules tend to diffuse into a hypertonic solution ([link]). Cells in a hypertonic solution will shrivel as water leaves the cell via osmosis. In contrast, a solution that has a lower concentration of solutes than another solution is said to be **hypotonic**, and water molecules tend to diffuse out of a hypotonic solution. Cells in a hypotonic solution will take on too much water and swell, with the risk of eventually bursting. A critical aspect of homeostasis in living things is to create an internal environment in which all of the body’s cells are in an isotonic solution. Various organ systems, particularly the kidneys, work to maintain this homeostasis.

Concentration of Solutions

A hypertonic solution has a solute concentration higher than another solution. An isotonic solution has a solute concentration equal to another solution. A hypotonic solution has a solute concentration lower than another solution.



Another mechanism besides diffusion to passively transport materials between compartments is filtration. Unlike diffusion of a substance from where it is more concentrated to less concentrated, filtration uses a hydrostatic pressure gradient that pushes the fluid—and the solutes within it—from a higher pressure area to a lower pressure area. Filtration is an extremely important process in the body. For example, the circulatory system uses filtration to move plasma and substances across the endothelial lining of capillaries and into surrounding tissues, supplying cells with the nutrients. Filtration pressure in the kidneys provides the mechanism to remove wastes from the bloodstream.

Active Transport

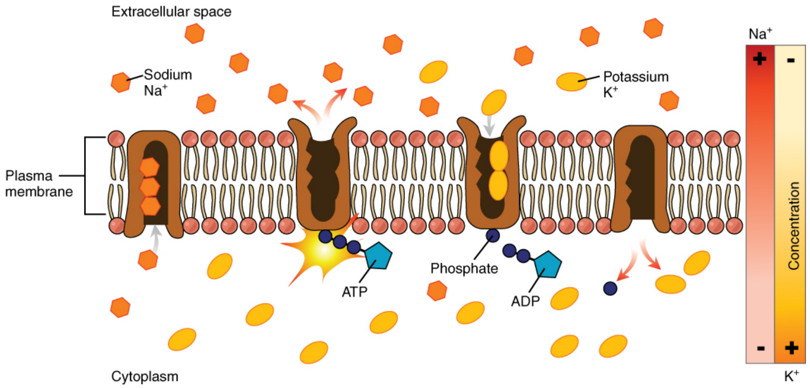
For all of the transport methods described above, the cell expends no energy. Membrane proteins that aid in the passive transport of substances do so without the use of ATP. During active transport, ATP is required to move a substance across a membrane, often with the help of protein carriers, and usually *against* its concentration gradient.

One of the most common types of active transport involves proteins that serve as pumps. The word “pump” probably conjures up thoughts of using energy to pump up the tire of a bicycle or a basketball. Similarly, energy from ATP is required for these membrane proteins to transport substances —molecules or ions—across the membrane, usually against their concentration gradients (from an area of low concentration to an area of high concentration).

The **sodium-potassium pump**, which is also called Na^+/K^+ ATPase, transports sodium out of a cell while moving potassium into the cell. The Na^+/K^+ pump is an important ion pump found in the membranes of many types of cells. These pumps are particularly abundant in nerve cells, which are constantly pumping out sodium ions and pulling in potassium ions to maintain an electrical gradient across their cell membranes. An **electrical gradient** is a difference in electrical charge across a space. In

the case of nerve cells, for example, the electrical gradient exists between the inside and outside of the cell, with the inside being negatively-charged (at around -70 mV) relative to the outside. The negative electrical gradient is maintained because each $Na+/K+$ pump moves three $Na+$ ions out of the cell and two $K+$ ions into the cell for each ATP molecule that is used ([link]). This process is so important for nerve cells that it accounts for the majority of their ATP usage.

Sodium-Potassium Pump
The sodium-potassium pump is found in many cell (plasma) membranes. Powered by ATP, the pump moves sodium and potassium ions in opposite directions, each against its concentration gradient. In a single cycle of the pump, three sodium ions are extruded from and two potassium ions are imported into the cell.



Active transport pumps can also work together with other active or passive transport systems to move substances across the membrane. For example, the sodium-potassium pump maintains a high

concentration of sodium ions outside of the cell. Therefore, if the cell needs sodium ions, all it has to do is open a passive sodium channel, as the concentration gradient of the sodium ions will drive them to diffuse into the cell. In this way, the action of an active transport pump (the sodium-potassium pump) powers the passive transport of sodium ions by creating a concentration gradient. When active transport powers the transport of another substance in this way, it is called secondary active transport.

Symporters are secondary active transporters that move two substances in the same direction. For example, the sodium-glucose symporter uses sodium ions to “pull” glucose molecules into the cell. Because cells store glucose for energy, glucose is typically at a higher concentration inside of the cell than outside. However, due to the action of the sodium-potassium pump, sodium ions will easily diffuse into the cell when the symporter is opened. The flood of sodium ions through the symporter provides the energy that allows glucose to move through the symporter and into the cell, against its concentration gradient.

Conversely, antiporters are secondary active transport systems that transport substances in opposite directions. For example, the sodium-hydrogen ion antiporter uses the energy from the inward flood of sodium ions to move hydrogen ions ($H+$) out of the cell. The sodium-hydrogen

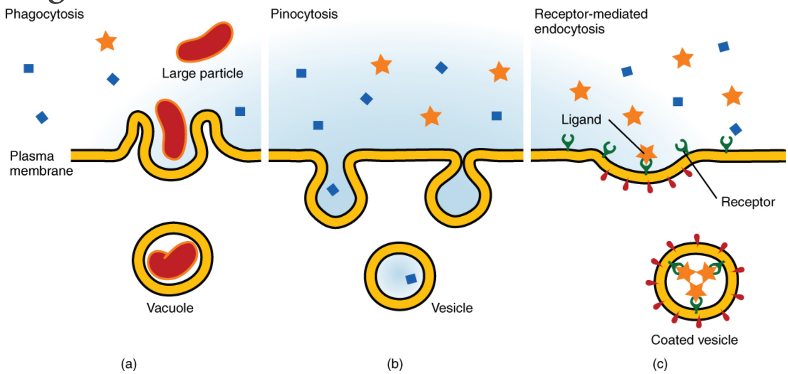
antiporter is used to maintain the pH of the cell's interior.

Other forms of active transport do not involve membrane carriers. **Endocytosis** (bringing “into the cell”) is the process of a cell ingesting material by enveloping it in a portion of its cell membrane, and then pinching off that portion of membrane ([link]). Once pinched off, the portion of membrane and its contents becomes an independent, intracellular vesicle. A **vesicle** is a membranous sac—a spherical and hollow organelle bounded by a lipid bilayer membrane. Endocytosis often brings materials into the cell that must to be broken down or digested. **Phagocytosis** (“cell eating”) is the endocytosis of large particles. Many immune cells engage in phagocytosis of invading pathogens. Like little Pac-men, their job is to patrol body tissues for unwanted matter, such as invading bacterial cells, phagocytize them, and digest them. In contrast to phagocytosis, **pinocytosis** (“cell drinking”) brings fluid containing dissolved substances into a cell through membrane vesicles.

Three Forms of Endocytosis

Endocytosis is a form of active transport in which a cell envelopes extracellular materials using its cell membrane. (a) In phagocytosis, which is relatively nonselective, the cell takes in a large particle. (b) In pinocytosis, the cell takes in small particles in fluid. (c) In contrast, receptor-mediated endocytosis is quite selective. When external receptors bind a

specific ligand, the cell responds by endocytosing the ligand.



Phagocytosis and pinocytosis take in large portions of extracellular material, and they are typically not highly selective in the substances they bring in. Cells regulate the endocytosis of specific substances via receptor-mediated endocytosis. **Receptor-mediated endocytosis** is endocytosis by a portion of the cell membrane that contains many receptors that are specific for a certain substance. Once the surface receptors have bound sufficient amounts of the specific substance (the receptor's ligand), the cell will endocytose the part of the cell membrane containing the receptor-ligand complexes. Iron, a required component of hemoglobin, is endocytosed by red blood cells in this way. Iron is bound to a protein called transferrin in the blood. Specific transferrin receptors on red blood cell surfaces bind the iron-transferrin molecules, and the cell endocytoses the receptor-ligand complexes.

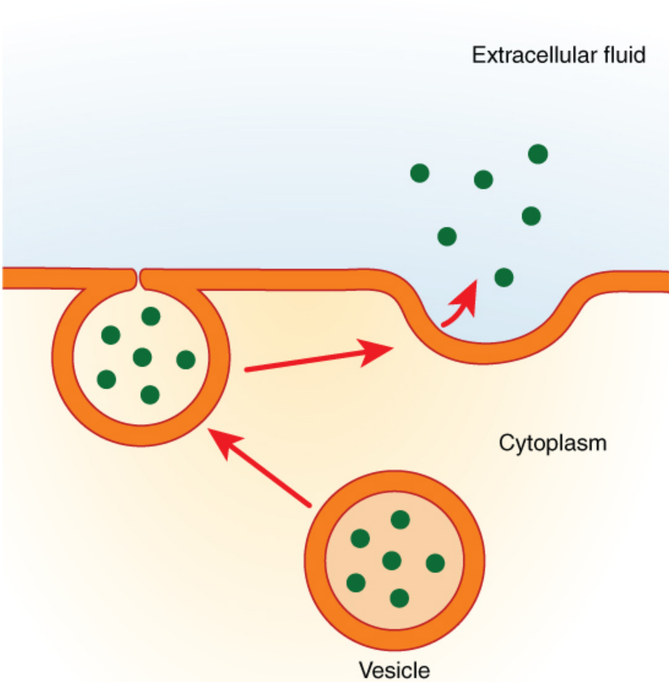
In contrast with endocytosis, **exocytosis** (taking

“out of the cell”) is the process of a cell exporting material using vesicular transport ([link]). Many cells manufacture substances that must be secreted, like a factory manufacturing a product for export. These substances are typically packaged into membrane-bound vesicles within the cell. When the vesicle membrane fuses with the cell membrane, the vesicle releases it contents into the interstitial fluid. The vesicle membrane then becomes part of the cell membrane. Cells of the stomach and pancreas produce and secrete digestive enzymes through exocytosis ([link]). Endocrine cells produce and secrete hormones that are sent throughout the body, and certain immune cells produce and secrete large amounts of histamine, a chemical important for immune responses.

Exocytosis

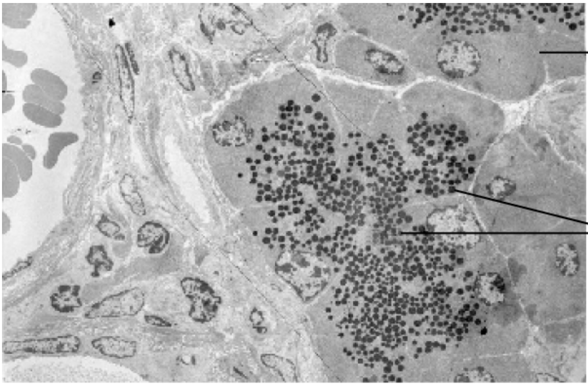
Exocytosis is much like endocytosis in reverse. Material destined for export is packaged into a vesicle inside the cell. The membrane of the vesicle fuses with the cell membrane, and the contents are released into the extracellular space.

Exocytosis



Pancreatic Cells' Enzyme Products

The pancreatic acinar cells produce and secrete many enzymes that digest food. The tiny black granules in this electron micrograph are secretory vesicles filled with enzymes that will be exported from the cells via exocytosis. LM × 2900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail.

Diseases of the…

Cell: Cystic Fibrosis

Cystic fibrosis (CF) affects approximately 30,000 people in the United States, with about 1,000 new cases reported each year. The genetic disease is most well known for its damage to the lungs, causing breathing difficulties and chronic lung

infections, but it also affects the liver, pancreas, and intestines. Only about 50 years ago, the prognosis for children born with CF was very grim—a life expectancy rarely over 10 years. Today, with advances in medical treatment, many CF patients live into their 30s.

The symptoms of CF result from a malfunctioning membrane ion channel called the cystic fibrosis transmembrane conductance regulator, or CFTR. In healthy people, the CFTR protein is an integral membrane protein that transports Cl^- ions out of the cell. In a person who has CF, the gene for the CFTR is mutated, thus, the cell manufactures a defective channel protein that typically is not incorporated into the membrane, but is instead degraded by the cell.

The CFTR requires ATP in order to function, making its Cl^- transport a form of active transport. This characteristic puzzled researchers for a long time because the Cl^- ions are actually flowing *down* their concentration gradient when transported out of cells. Active transport generally pumps ions *against* their concentration gradient, but the CFTR presents an exception to this rule.

In normal lung tissue, the movement of Cl^- out of the cell maintains a Cl^--rich, negatively charged environment immediately outside of the cell. This is particularly important in the epithelial lining of the respiratory system. Respiratory epithelial cells secrete mucus, which serves to trap dust, bacteria, and other debris. A cilium (plural = cilia) is one of

the hair-like appendages found on certain cells. Cilia on the epithelial cells move the mucus and its trapped particles up the airways away from the lungs and toward the outside. In order to be effectively moved upward, the mucus cannot be too viscous; rather it must have a thin, watery consistency. The transport of Cl^- and the maintenance of an electronegative environment outside of the cell attract positive ions such as Na^+ to the extracellular space. The accumulation of both Cl^- and Na^+ ions in the extracellular space creates solute-rich mucus, which has a low concentration of water molecules. As a result, through osmosis, water moves from cells and extracellular matrix into the mucus, "thinning" it out. This is how, in a normal respiratory system, the mucus is kept sufficiently watered-down to be propelled out of the respiratory system.

If the CFTR channel is absent, Cl^- ions are not transported out of the cell in adequate numbers, thus preventing them from drawing positive ions. The absence of ions in the secreted mucus results in the lack of a normal water concentration gradient. Thus, there is no osmotic pressure pulling water into the mucus. The resulting mucus is thick and sticky, and the ciliated epithelia cannot effectively remove it from the respiratory system. Passageways in the lungs become blocked with mucus, along with the debris it carries. Bacterial infections occur more easily because bacterial cells are not effectively carried away from the lungs.

Chapter Review

The cell membrane provides a barrier around the cell, separating its internal components from the extracellular environment. It is composed of a phospholipid bilayer, with hydrophobic internal lipid “tails” and hydrophilic external phosphate “heads.” Various membrane proteins are scattered throughout the bilayer, both inserted within it and attached to it peripherally. The cell membrane is selectively permeable, allowing only a limited number of materials to diffuse through its lipid bilayer. All materials that cross the membrane do so using passive (non energy-requiring) or active (energy-requiring) transport processes. During passive transport, materials move by simple diffusion or by facilitated diffusion through the membrane, down their concentration gradient. Water passes through the membrane in a diffusion process called osmosis. During active transport, energy is expended to assist material movement across the membrane in a direction against their concentration gradient. Active transport may take place with the help of protein pumps or through the use of vesicles.

Interactive Link Questions

Visit this link to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?

Higher temperatures speed up diffusion because molecules have more kinetic energy at higher temperatures.

Review Questions

Because they are embedded within the membrane, ion channels are examples of ______.

1. receptor proteins
2. integral proteins
3. peripheral proteins
4. glycoproteins

B

The diffusion of substances within a solution tends to move those substances ______ their ______ gradient.

1. up; electrical
2. up; electrochemical
3. down; pressure
4. down; concentration

D

Ion pumps and phagocytosis are both examples of ______.

1. endocytosis
2. passive transport
3. active transport
4. facilitated diffusion

C

Choose the answer that best completes the following analogy: Diffusion is to ______ as endocytosis is to ______.

1. filtration; phagocytosis
2. osmosis; pinocytosis
3. solutes; fluid
4. gradient; chemical energy

B

Critical Thinking Questions

What materials can easily diffuse through the lipid bilayer, and why?

Only materials that are relatively small and nonpolar can easily diffuse through the lipid bilayer. Large particles cannot fit in between the individual phospholipids that are packed together, and polar molecules are repelled by the hydrophobic/nonpolar lipids that line the inside of the bilayer.

Why is receptor-mediated endocytosis said to be more selective than phagocytosis or pinocytosis?

Receptor-mediated endocytosis is more selective because the substances that are brought into the cell are the specific ligands that could bind to the receptors being endocytosed. Phagocytosis or pinocytosis, on the other hand, have no such receptor-ligand specificity, and bring in whatever materials happen to be close to the membrane when it is

enveloped.

What do osmosis, diffusion, filtration, and the movement of ions away from like charge all have in common? In what way do they differ?

These four phenomena are similar in the sense that they describe the movement of substances down a particular type of gradient. Osmosis and diffusion involve the movement of water and other substances down their concentration gradients, respectively. Filtration describes the movement of particles down a pressure gradient, and the movement of ions away from like charge describes their movement down their electrical gradient.

Glossary

active transport
: form of transport across the cell membrane that requires input of cellular energy

amphipathic
: describes a molecule that exhibits a difference in polarity between its two ends, resulting in a difference in water solubility

cell membrane

membrane surrounding all animal cells, composed of a lipid bilayer interspersed with various molecules; also known as plasma membrane

channel protein
: membrane-spanning protein that has an inner pore which allows the passage of one or more substances

concentration gradient
: difference in the concentration of a substance between two regions

diffusion
: movement of a substance from an area of higher concentration to one of lower concentration

electrical gradient
: difference in the electrical charge (potential) between two regions

endocytosis
: import of material into the cell by formation of a membrane-bound vesicle

exocytosis
: export of a substance out of a cell by formation of a membrane-bound vesicle

extracellular fluid (ECF)

fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluid found in other reservoirs in the body

facilitated diffusion
: diffusion of a substance with the aid of a membrane protein

glycocalyx
: coating of sugar molecules that surrounds the cell membrane

glycoprotein
: protein that has one or more carbohydrates attached

hydrophilic
: describes a substance or structure attracted to water

hydrophobic
: describes a substance or structure repelled by water

hypertonic
: describes a solution concentration that is higher than a reference concentration

hypotonic
: describes a solution concentration that is lower than a reference concentration

integral protein

membrane-associated protein that spans the entire width of the lipid bilayer

interstitial fluid (IF)
: fluid in the small spaces between cells not contained within blood vessels

intracellular fluid (ICF)
: fluid in the cytosol of cells

isotonic
: describes a solution concentration that is the same as a reference concentration

ligand
: molecule that binds with specificity to a specific receptor molecule

osmosis
: diffusion of water molecules down their concentration gradient across a selectively permeable membrane

passive transport
: form of transport across the cell membrane that does not require input of cellular energy

peripheral protein
: membrane-associated protein that does not span the width of the lipid bilayer, but is attached peripherally to integral proteins, membrane lipids, or other components of the

membrane

phagocytosis
endocytosis of large particles

pinocytosis
endocytosis of fluid

receptor
protein molecule that contains a binding site for another specific molecule (called a ligand)

receptor-mediated endocytosis
endocytosis of ligands attached to membrane-bound receptors

selective permeability
feature of any barrier that allows certain substances to cross but excludes others

sodium-potassium pump
(also, Na^+/K^+ ATP-ase) membrane-embedded protein pump that uses ATP to move Na^+ out of a cell and K^+ into the cell

vesicle
membrane-bound structure that contains materials within or outside of the cell

The Cytoplasm and Cellular Organelles

By the end of this section, you will be able to:

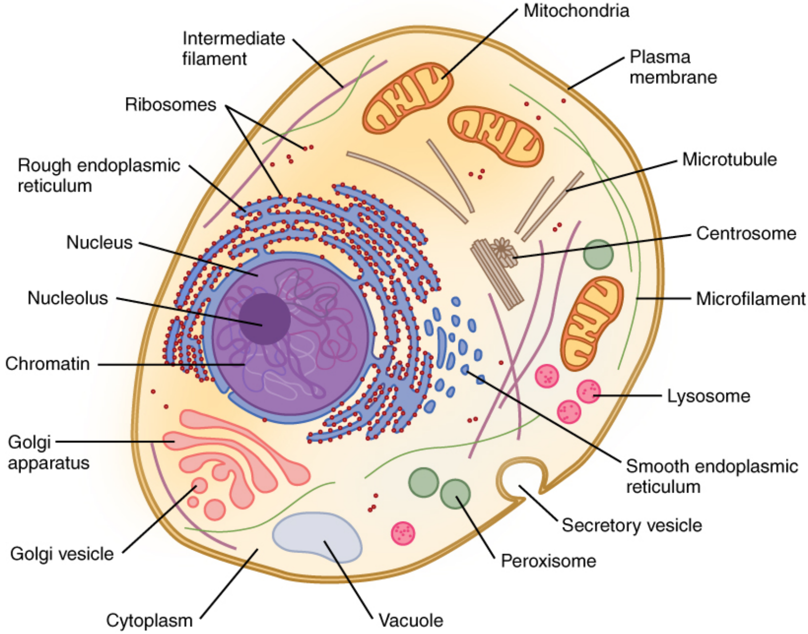
- Describe the structure and function of the cellular organelles associated with the endomembrane system, including the endoplasmic reticulum, Golgi apparatus, and lysosomes
- Describe the structure and function of mitochondria and peroxisomes
- Explain the three components of the cytoskeleton, including their composition and functions

Now that you have learned that the cell membrane surrounds all cells, you can dive inside of a prototypical human cell to learn about its internal components and their functions. All living cells in multicellular organisms contain an internal cytoplasmic compartment, and a nucleus within the cytoplasm. **Cytosol**, the jelly-like substance within the cell, provides the fluid medium necessary for biochemical reactions. Eukaryotic cells, including all animal cells, also contain various cellular organelles. An **organelle** ("little organ") is one of several different types of membrane-enclosed bodies in the cell, each performing a unique function. Just as the various bodily organs work together in harmony to perform all of a human's functions, the many different cellular organelles work together to keep the cell healthy and performing all of its important

functions. The organelles and cytosol, taken together, compose the cell's **cytoplasm**. The **nucleus** is a cell's central organelle, which contains the cell's DNA ([link]).

Prototypical Human Cell

While this image is not indicative of any one particular human cell, it is a prototypical example of a cell containing the primary organelles and internal structures.



Organelles of the Endomembrane System

A set of three major organelles together form a system within the cell called the endomembrane system. These organelles work together to perform various cellular jobs, including the task of

producing, packaging, and exporting certain cellular products. The organelles of the endomembrane system include the endoplasmic reticulum, Golgi apparatus, and vesicles.

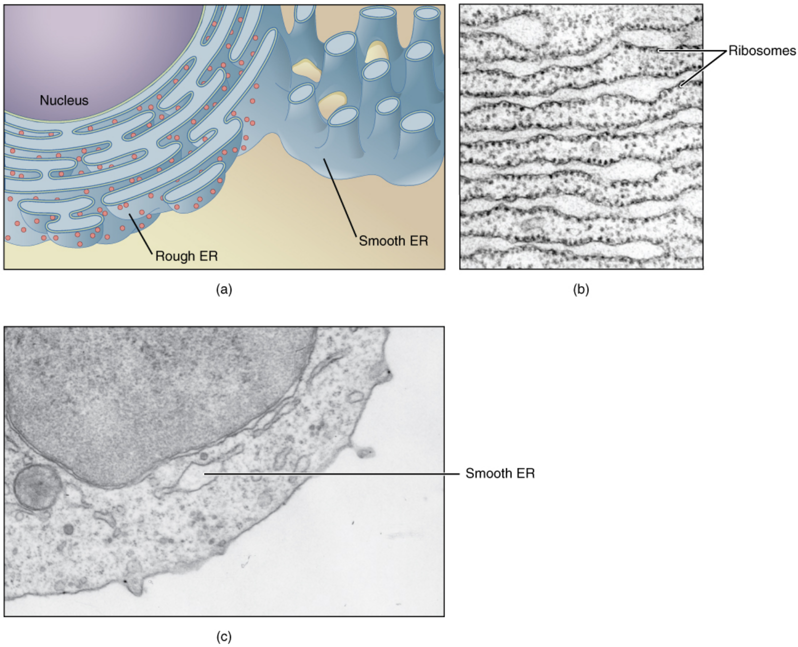
Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is a system of channels that is continuous with the nuclear membrane (or "envelope") covering the nucleus and composed of the same lipid bilayer material. The ER can be thought of as a series of winding thoroughfares similar to the waterway canals in Venice. The ER provides passages throughout much of the cell that function in transporting, synthesizing, and storing materials. The winding structure of the ER results in a large membranous surface area that supports its many functions ([link]).

Endoplasmic Reticulum (ER)

(a) The ER is a winding network of thin membranous sacs found in close association with the cell nucleus. The smooth and rough endoplasmic reticula are very different in appearance and function (source: mouse tissue). (b) Rough ER is studded with numerous ribosomes, which are sites of protein synthesis (source: mouse tissue). EM × 110,000. (c) Smooth ER synthesizes phospholipids, steroid hormones, regulates the concentration of cellular Ca^{++}, metabolizes some carbohydrates, and breaks down certain toxins (source: mouse tissue).

EM × 110,510. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)



Endoplasmic reticulum can exist in two forms: rough ER and smooth ER. These two types of ER perform some very different functions and can be found in very different amounts depending on the type of cell. Rough ER (RER) is so-called because its membrane is dotted with embedded granules—organelles called ribosomes, giving the RER a bumpy appearance. A **ribosome** is an organelle that serves as the site of protein synthesis. It is composed of two ribosomal RNA subunits that wrap around mRNA to start the process of translation, followed by protein synthesis. Smooth ER (SER) lacks these ribosomes.

One of the main functions of the smooth ER is in the synthesis of lipids. The smooth ER synthesizes phospholipids, the main component of biological membranes, as well as steroid hormones. For this reason, cells that produce large quantities of such hormones, such as those of the female ovaries and male testes, contain large amounts of smooth ER. In addition to lipid synthesis, the smooth ER also sequesters (i.e., stores) and regulates the concentration of cellular Ca^{++}, a function extremely important in cells of the nervous system where Ca^{++} is the trigger for neurotransmitter release. The smooth ER additionally metabolizes some carbohydrates and performs a detoxification role, breaking down certain toxins.

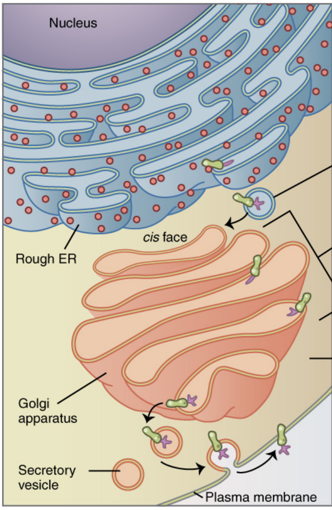
In contrast with the smooth ER, the primary job of the rough ER is the synthesis and modification of proteins destined for the cell membrane or for export from the cell. For this protein synthesis, many ribosomes attach to the ER (giving it the studded appearance of rough ER). Typically, a protein is synthesized within the ribosome and released inside the channel of the rough ER, where sugars can be added to it (by a process called glycosylation) before it is transported within a vesicle to the next stage in the packaging and shipping process: the Golgi apparatus.

The Golgi Apparatus

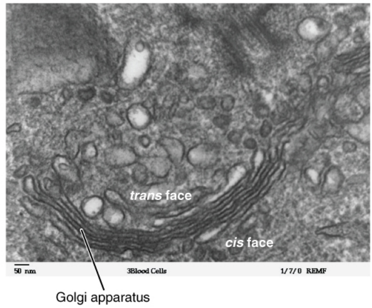
The **Golgi apparatus** is responsible for sorting, modifying, and shipping off the products that come from the rough ER, much like a post-office. The Golgi apparatus looks like stacked flattened discs, almost like stacks of oddly shaped pancakes. Like the ER, these discs are membranous. The Golgi apparatus has two distinct sides, each with a different role. One side of the apparatus receives products in vesicles. These products are sorted through the apparatus, and then they are released from the opposite side after being repackaged into new vesicles. If the product is to be exported from the cell, the vesicle migrates to the cell surface and fuses to the cell membrane, and the cargo is secreted ([link]).

Golgi Apparatus

(a) The Golgi apparatus manipulates products from the rough ER, and also produces new organelles called lysosomes. Proteins and other products of the ER are sent to the Golgi apparatus, which organizes, modifies, packages, and tags them. Some of these products are transported to other areas of the cell and some are exported from the cell through exocytosis. Enzymatic proteins are packaged as new lysosomes (or packaged and sent for fusion with existing lysosomes). (b) An electron micrograph of the Golgi apparatus.



(a)



(b)

Lysosomes

Some of the protein products packaged by the Golgi include digestive enzymes that are meant to remain inside the cell for use in breaking down certain materials. The enzyme-containing vesicles released by the Golgi may form new lysosomes, or fuse with existing, lysosomes. A **lysosome** is an organelle that contains enzymes that break down and digest unneeded cellular components, such as a damaged organelle. (A lysosome is similar to a wrecking crew that takes down old and unsound buildings in a neighborhood.) **Autophagy** ("self-eating") is the process of a cell digesting its own structures. Lysosomes are also important for breaking down foreign material. For example, when certain immune defense cells (white blood cells) phagocytize bacteria, the bacterial cell is

transported into a lysosome and digested by the enzymes inside. As one might imagine, such phagocytic defense cells contain large numbers of lysosomes.

Under certain circumstances, lysosomes perform a more grand and dire function. In the case of damaged or unhealthy cells, lysosomes can be triggered to open up and release their digestive enzymes into the cytoplasm of the cell, killing the cell. This “self-destruct” mechanism is called **autolysis**, and makes the process of cell death controlled (a mechanism called “apoptosis”).

Watch this video to learn about the endomembrane system, which includes the rough and smooth ER and the Golgi body as well as lysosomes and vesicles. What is the primary role of the endomembrane system?

Organelles for Energy Production and Detoxification

In addition to the jobs performed by the endomembrane system, the cell has many other important functions. Just as you must consume nutrients to provide yourself with energy, so must each of your cells take in nutrients, some of which convert to chemical energy that can be used to power biochemical reactions. Another important function of the cell is detoxification. Humans take in all sorts of toxins from the environment and also produce harmful chemicals as byproducts of cellular processes. Cells called hepatocytes in the liver detoxify many of these toxins.

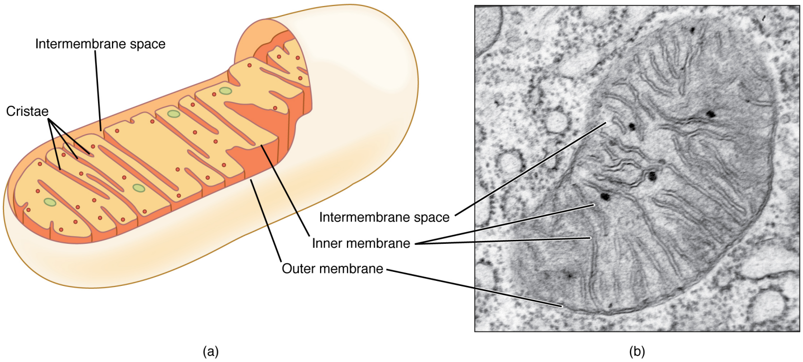
Mitochondria

A **mitochondrion** (plural = mitochondria) is a membranous, bean-shaped organelle that is the “energy transformer” of the cell. Mitochondria consist of an outer lipid bilayer membrane as well as an additional inner lipid bilayer membrane ([link]). The inner membrane is highly folded into winding structures with a great deal of surface area, called cristae. It is along this inner membrane that a series of proteins, enzymes, and other molecules perform the biochemical reactions of cellular respiration.

These reactions convert energy stored in nutrient molecules (such as glucose) into adenosine triphosphate (ATP), which provides usable cellular energy to the cell. Cells use ATP constantly, and so the mitochondria are constantly at work. Oxygen molecules are required during cellular respiration, which is why you must constantly breathe it in. One of the organ systems in the body that uses huge amounts of ATP is the muscular system because ATP is required to sustain muscle contraction. As a result, muscle cells are packed full of mitochondria. Nerve cells also need large quantities of ATP to run their sodium-potassium pumps. Therefore, an individual neuron will be loaded with over a thousand mitochondria. On the other hand, a bone cell, which is not nearly as metabolically-active, might only have a couple hundred mitochondria.

Mitochondrion

The mitochondria are the energy-conversion factories of the cell. (a) A mitochondrion is composed of two separate lipid bilayer membranes. Along the inner membrane are various molecules that work together to produce ATP, the cell's major energy currency. (b) An electron micrograph of mitochondria. EM × 236,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

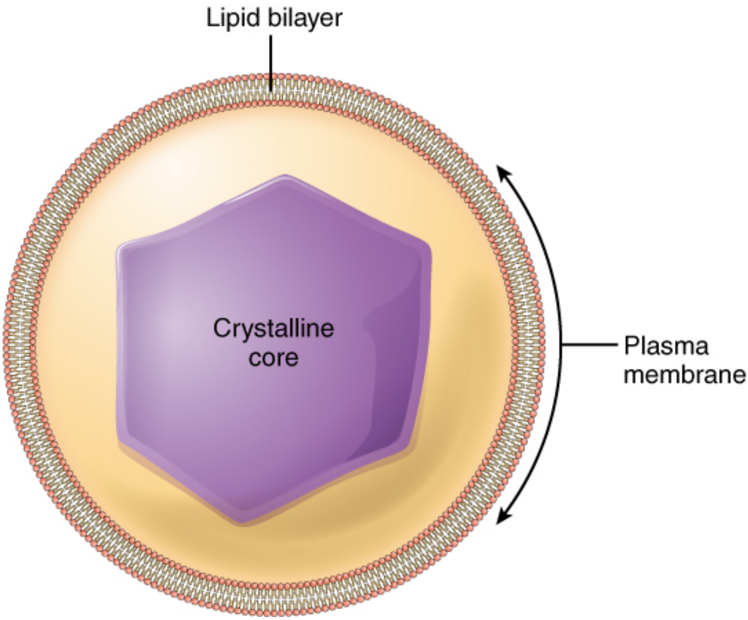


Peroxisomes

Like lysosomes, a **peroxisome** is a membrane-bound cellular organelle that contains mostly enzymes ([link]). Peroxisomes perform a couple of different functions, including lipid metabolism and chemical detoxification. In contrast to the digestive enzymes found in lysosomes, the enzymes within peroxisomes serve to transfer hydrogen atoms from various molecules to oxygen, producing hydrogen peroxide (H_2O_2). In this way, peroxisomes neutralize poisons such as alcohol. In order to appreciate the importance of peroxisomes, it is necessary to understand the concept of reactive oxygen species.

Peroxisome

Peroxisomes are membrane-bound organelles that contain an abundance of enzymes for detoxifying harmful substances and lipid metabolism.



Reactive oxygen species (ROS) such as peroxides and free radicals are the highly reactive products of many normal cellular processes, including the mitochondrial reactions that produce ATP and oxygen metabolism. Examples of ROS include the hydroxyl radical OH, H_2O_2, and superoxide (O_2^-). Some ROS are important for certain cellular functions, such as cell signaling processes and immune responses against foreign substances. Free radicals are reactive because they contain free unpaired electrons; they can easily oxidize other molecules throughout the cell, causing cellular damage and even cell death. Free radicals are thought to play a role in many destructive processes in the body, from cancer to coronary artery disease.

Peroxisomes, on the other hand, oversee reactions

that neutralize free radicals. Peroxisomes produce large amounts of the toxic H_2O_2 in the process, but peroxisomes contain enzymes that convert H_2O_2 into water and oxygen. These byproducts are safely released into the cytoplasm. Like miniature sewage treatment plants, peroxisomes neutralize harmful toxins so that they do not wreak havoc in the cells. The liver is the organ primarily responsible for detoxifying the blood before it travels throughout the body, and liver cells contain an exceptionally high number of peroxisomes.

Defense mechanisms such as detoxification within the peroxisome and certain cellular antioxidants serve to neutralize many of these molecules. Some vitamins and other substances, found primarily in fruits and vegetables, have antioxidant properties. Antioxidants work by being oxidized themselves, halting the destructive reaction cascades initiated by the free radicals. Sometimes though, ROS accumulate beyond the capacity of such defenses.

Oxidative stress is the term used to describe damage to cellular components caused by ROS. Due to their characteristic unpaired electrons, ROS can set off chain reactions where they remove electrons from other molecules, which then become oxidized and reactive, and do the same to other molecules, causing a chain reaction. ROS can cause permanent damage to cellular lipids, proteins, carbohydrates, and nucleic acids. Damaged DNA can lead to genetic

mutations and even cancer. A **mutation** is a change in the nucleotide sequence in a gene within a cell's DNA, potentially altering the protein coded by that gene. Other diseases believed to be triggered or exacerbated by ROS include Alzheimer's disease, cardiovascular diseases, diabetes, Parkinson's disease, arthritis, Huntington's disease, and schizophrenia, among many others. It is noteworthy that these diseases are largely age-related. Many scientists believe that oxidative stress is a major contributor to the aging process.

Aging and the…

Cell: The Free Radical Theory

The free radical theory on aging was originally proposed in the 1950s, and still remains under debate. Generally speaking, the free radical theory of aging suggests that accumulated cellular damage from oxidative stress contributes to the physiological and anatomical effects of aging. There are two significantly different versions of this theory: one states that the aging process itself is a result of oxidative damage, and the other states that oxidative damage causes age-related disease and disorders. The latter version of the theory is more widely accepted than the former. However, many lines of evidence suggest that oxidative damage does contribute to the aging process. Research has shown that reducing oxidative

damage can result in a longer lifespan in certain organisms such as yeast, worms, and fruit flies. Conversely, increasing oxidative damage can shorten the lifespan of mice and worms. Interestingly, a manipulation called calorie-restriction (moderately restricting the caloric intake) has been shown to increase life span in some laboratory animals. It is believed that this increase is at least in part due to a reduction of oxidative stress. However, a long-term study of primates with calorie-restriction showed no increase in their lifespan. A great deal of additional research will be required to better understand the link between reactive oxygen species and aging.

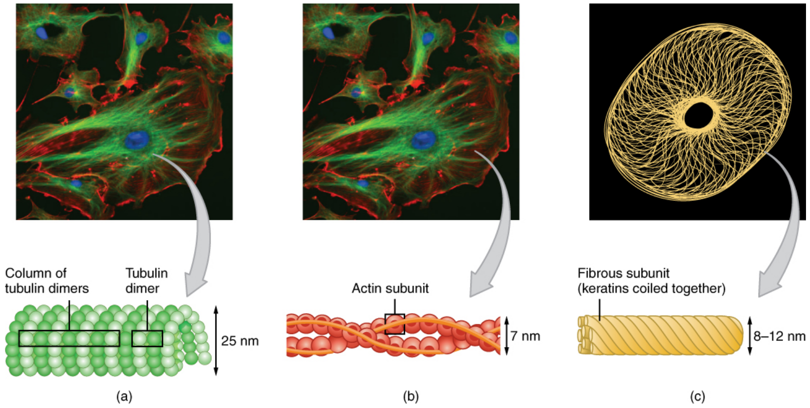
The Cytoskeleton

Much like the bony skeleton structurally supports the human body, the cytoskeleton helps the cells to maintain their structural integrity. The **cytoskeleton** is a group of fibrous proteins that provide structural support for cells, but this is only one of the functions of the cytoskeleton. Cytoskeletal components are also critical for cell motility, cell reproduction, and transportation of substances within the cell.

The cytoskeleton forms a complex thread-like network throughout the cell consisting of three different kinds of protein-based filaments: microfilaments, intermediate filaments, and microtubules ([link]). The thickest of the three is the **microtubule**, a structural filament composed of subunits of a protein called tubulin. Microtubules maintain cell shape and structure, help resist compression of the cell, and play a role in positioning the organelles within the cell. Microtubules also make up two types of cellular appendages important for motion: cilia and flagella. **Cilia** are found on many cells of the body, including the epithelial cells that line the airways of the respiratory system. Cilia move rhythmically; they beat constantly, moving waste materials such as dust, mucus, and bacteria upward through the airways, away from the lungs and toward the mouth. Beating cilia on cells in the female fallopian tubes move egg cells from the ovary towards the uterus. A **flagellum** (plural = flagella) is an appendage larger than a cilium and specialized for cell locomotion. The only flagellated cell in humans is the sperm cell that must propel itself towards female egg cells.

The Three Components of the Cytoskeleton

The cytoskeleton consists of (a) microtubules, (b) microfilaments, and (c) intermediate filaments. The cytoskeleton plays an important role in maintaining cell shape and structure, promoting cellular movement, and aiding cell division.



A very important function of microtubules is to set the paths (somewhat like railroad tracks) along which the genetic material can be pulled (a process requiring ATP) during cell division, so that each new daughter cell receives the appropriate set of chromosomes. Two short, identical microtubule structures called centrioles are found near the nucleus of cells. A **centriole** can serve as the cellular origin point for microtubules extending outward as cilia or flagella or can assist with the separation of DNA during cell division. Microtubules grow out from the centrioles by adding more tubulin subunits, like adding additional links to a chain.

In contrast with microtubules, the **microfilament** is a thinner type of cytoskeletal filament (see [link]**b**). Actin, a protein that forms chains, is the primary component of these microfilaments. Actin fibers, twisted chains of actin filaments, constitute a large component of muscle tissue and, along with the

protein myosin, are responsible for muscle contraction. Like microtubules, actin filaments are long chains of single subunits (called actin subunits). In muscle cells, these long actin strands, called thin filaments, are “pulled” by thick filaments of the myosin protein to contract the cell.

Actin also has an important role during cell division. When a cell is about to split in half during cell division, actin filaments work with myosin to create a cleavage furrow that eventually splits the cell down the middle, forming two new cells from the original cell.

The final cytoskeletal filament is the intermediate filament. As its name would suggest, an **intermediate filament** is a filament intermediate in thickness between the microtubules and microfilaments (see [link]**c**). Intermediate filaments are made up of long fibrous subunits of a protein called keratin that are wound together like the threads that compose a rope. Intermediate filaments, in concert with the microtubules, are important for maintaining cell shape and structure. Unlike the microtubules, which resist compression, intermediate filaments resist tension—the forces that pull apart cells. There are many cases in which cells are prone to tension, such as when epithelial cells of the skin are compressed, tugging them in different directions. Intermediate filaments help anchor organelles together within a cell and also

link cells to other cells by forming special cell-to-cell junctions.

Chapter Review

The internal environmental of a living cell is made up of a fluid, jelly-like substance called cytosol, which consists mainly of water, but also contains various dissolved nutrients and other molecules. The cell contains an array of cellular organelles, each one performing a unique function and helping to maintain the health and activity of the cell. The cytosol and organelles together compose the cell's cytoplasm. Most organelles are surrounded by a lipid membrane similar to the cell membrane of the cell. The endoplasmic reticulum (ER), Golgi apparatus, and lysosomes share a functional connectivity and are collectively referred to as the endomembrane system. There are two types of ER: smooth and rough. While the smooth ER performs many functions, including lipid synthesis and ion storage, the rough ER is mainly responsible for protein synthesis using its associated ribosomes. The rough ER sends newly made proteins to the Golgi apparatus where they are modified and packaged for delivery to various locations within or outside of the cell. Some of these protein products are enzymes destined to break down unwanted material and are packaged as lysosomes for use inside the cell.

Cells also contain mitochondria and peroxisomes, which are the organelles responsible for producing the cell's energy supply and detoxifying certain chemicals, respectively. Biochemical reactions within mitochondria transform energy-carrying molecules into the usable form of cellular energy known as ATP. Peroxisomes contain enzymes that transform harmful substances such as free radicals into oxygen and water. Cells also contain a miniaturized "skeleton" of protein filaments that extend throughout its interior. Three different kinds of filaments compose this cytoskeleton (in order of increasing thickness): microfilaments, intermediate filaments, and microtubules. Each cytoskeletal component performs unique functions as well as provides a supportive framework for the cell.

Interactive Link Questions

Watch this video to learn about the endomembrane system, which includes the rough and smooth ER and the Golgi body as well as lysosomes and vesicles. What is the primary role of the endomembrane system?

Processing, packaging, and moving materials manufactured by the cell.

Review Questions

Choose the term that best completes the following analogy: Cytoplasm is to cytosol as a swimming pool containing chlorine and flotation toys is to ______.

1. the walls of the pool
2. the chlorine
3. the flotation toys
4. the water

D

The rough ER has its name due to what associated structures?

1. Golgi apparatus
2. ribosomes
3. lysosomes
4. proteins

B

Which of the following is a function of the rough ER?

1. production of proteins
2. detoxification of certain substances
3. synthesis of steroid hormones
4. regulation of intracellular calcium concentration

A

Which of the following is a feature common to all three components of the cytoskeleton?

1. They all serve to scaffold the organelles within the cell.
2. They are all characterized by roughly the same diameter.
3. They are all polymers of protein subunits.
4. They all help the cell resist compression and tension.

C

Which of the following organelles produces large quantities of ATP when both glucose and oxygen are available to the cell?

1. mitochondria
2. peroxisomes
3. lysosomes
4. ER

A

Critical Thinking Questions

Explain why the structure of the ER, mitochondria, and Golgi apparatus assist their respective functions.

The structure of the Golgi apparatus is suited to its function because it is a series of flattened membranous discs; substances are modified and packaged in sequential steps as they travel from one disc to the next. The structure of Golgi apparatus also involves a receiving face and a sending face, which organize cellular products as they enter and leave the Golgi apparatus. The ER and the mitochondria both have structural specializations that increase their surface area. In the mitochondria, the inner membrane is extensively folded, which increases surface area for ATP production.

Likewise, the ER is elaborately wound throughout the cell, increasing its surface area for functions like lipid synthesis, Ca^{++} storage, and protein synthesis.

Compare and contrast lysosomes with peroxisomes: name at least two similarities and one difference.

Peroxisomes and lysosomes are both cellular organelles bound by lipid bilayer membranes, and they both contain many enzymes. However, peroxisomes contain enzymes that detoxify substances by transferring hydrogen atoms and producing H_2O_2, whereas the enzymes in lysosomes function to break down and digest various unwanted materials.

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Glossary

autolysis
: breakdown of cells by their own enzymatic action

autophagy
: lysosomal breakdown of a cell's own components

centriole
: small, self-replicating organelle that provides the origin for microtubule growth and moves DNA during cell division

cilia
: small appendage on certain cells formed by microtubules and modified for movement of materials across the cellular surface

cytoplasm
: internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials

cytoskeleton
: "skeleton" of a cell; formed by rod-like proteins that support the cell's shape and provide, among other functions, locomotive abilities

cytosol
: clear, semi-fluid medium of the cytoplasm, made up mostly of water

endoplasmic reticulum (ER)
: cellular organelle that consists of interconnected membrane-bound tubules, which may or may not be associated with ribosomes (rough type or smooth type, respectively)

flagellum
: appendage on certain cells formed by microtubules and modified for movement

Golgi apparatus
: cellular organelle formed by a series of flattened, membrane-bound sacs that functions in protein modification, tagging, packaging, and transport

intermediate filament
: type of cytoskeletal filament made of keratin, characterized by an intermediate thickness, and playing a role in resisting cellular tension

lysosome
: membrane-bound cellular organelle originating from the Golgi apparatus and containing digestive enzymes

microfilament

the thinnest of the cytoskeletal filaments; composed of actin subunits that function in muscle contraction and cellular structural support

microtubule
: the thickest of the cytoskeletal filaments, composed of tubulin subunits that function in cellular movement and structural support

mitochondrion
: one of the cellular organelles bound by a double lipid bilayer that function primarily in the production of cellular energy (ATP)

mutation
: change in the nucleotide sequence in a gene within a cell’s DNA

nucleus
: cell’s central organelle; contains the cell’s DNA

organelle
: any of several different types of membrane-enclosed specialized structures in the cell that perform specific functions for the cell

peroxisome
: membrane-bound organelle that contains enzymes primarily responsible for detoxifying harmful substances

reactive oxygen species (ROS)
: a group of extremely reactive peroxides and oxygen-containing radicals that may contribute to cellular damage

ribosome
: cellular organelle that functions in protein synthesis

The Nucleus and DNA Replication

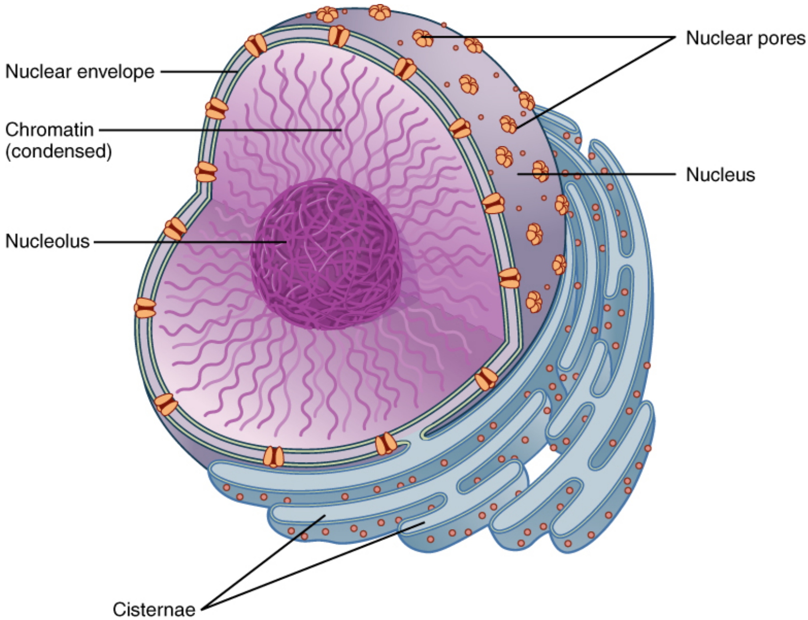
By the end of this section, you will be able to:

- Describe the structure and features of the nuclear membrane
- List the contents of the nucleus
- Explain the organization of the DNA molecule within the nucleus
- Describe the process of DNA replication

The nucleus is the largest and most prominent of a cell’s organelles ([link]). The nucleus is generally considered the control center of the cell because it stores all of the genetic instructions for manufacturing proteins. Interestingly, some cells in the body, such as muscle cells, contain more than one nucleus ([link]), which is known as multinucleated. Other cells, such as mammalian red blood cells (RBCs), do not contain nuclei at all. RBCs eject their nuclei as they mature, making space for the large numbers of hemoglobin molecules that carry oxygen throughout the body ([link]). Without nuclei, the life span of RBCs is short, and so the body must produce new ones constantly.

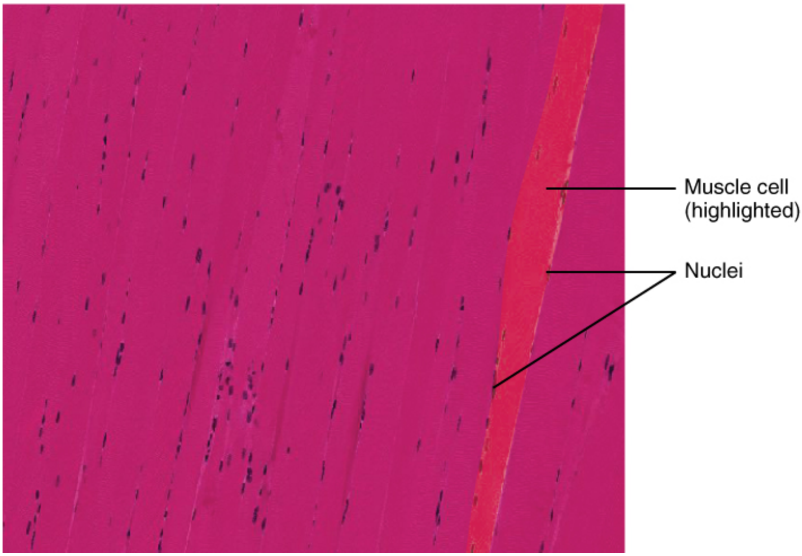
The Nucleus

The nucleus is the control center of the cell. The nucleus of living cells contains the genetic material that determines the entire structure and function of that cell.



Multinucleate Muscle Cell

Unlike cardiac muscle cells and smooth muscle cells, which have a single nucleus, a skeletal muscle cell contains many nuclei, and is referred to as "multinucleated." These muscle cells are long and fibrous (often referred to as muscle fibers). During development, many smaller cells fuse to form a mature muscle fiber. The nuclei of the fused cells are conserved in the mature cell, thus imparting a multinucleate characteristic to mature muscle cells. LM × 104.3. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

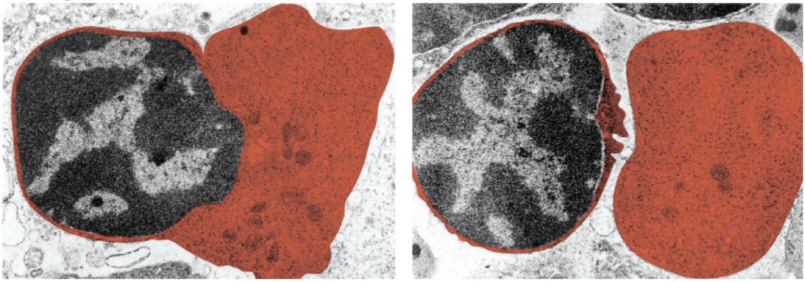


View the University of Michigan WebScope to explore the tissue sample in greater detail.

Red Blood Cell Extruding Its Nucleus

Mature red blood cells lack a nucleus. As they mature, erythroblasts extrude their nucleus, making

room for more hemoglobin. The two panels here show an erythroblast before and after ejecting its nucleus, respectively. (credit: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail.

Inside the nucleus lies the blueprint that dictates everything a cell will do and all of the products it will make. This information is stored within DNA. The nucleus sends “commands” to the cell via

molecular messengers that translate the information from DNA. Each cell in your body (with the exception of germ cells) contains the complete set of your DNA. When a cell divides, the DNA must be duplicated so that the each new cell receives a full complement of DNA. The following section will explore the structure of the nucleus and its contents, as well as the process of DNA replication.

Organization of the Nucleus and Its DNA

Like most other cellular organelles, the nucleus is surrounded by a membrane called the **nuclear envelope**. This membranous covering consists of two adjacent lipid bilayers with a thin fluid space in between them. Spanning these two bilayers are nuclear pores. A **nuclear pore** is a tiny passageway for the passage of proteins, RNA, and solutes between the nucleus and the cytoplasm. Proteins called pore complexes lining the nuclear pores regulate the passage of materials into and out of the nucleus.

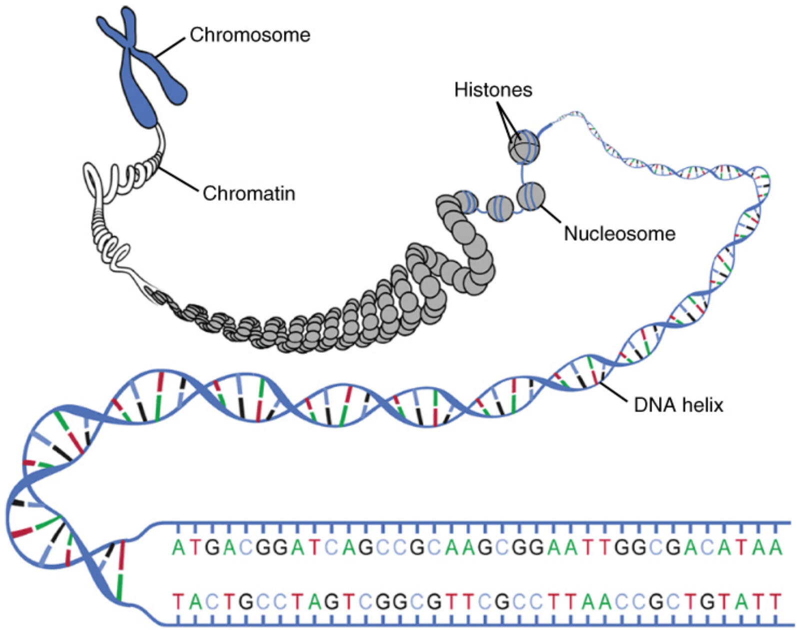
Inside the nuclear envelope is a gel-like nucleoplasm with solutes that include the building blocks of nucleic acids. There also can be a dark-staining mass often visible under a simple light microscope, called a **nucleolus** (plural = nucleoli). The nucleolus is a region of the nucleus that is responsible for manufacturing the RNA necessary for construction

of ribosomes. Once synthesized, newly made ribosomal subunits exit the cell’s nucleus through the nuclear pores.

The genetic instructions that are used to build and maintain an organism are arranged in an orderly manner in strands of DNA. Within the nucleus are threads of **chromatin** composed of DNA and associated proteins ([link]). Along the chromatin threads, the DNA is wrapped around a set of **histone** proteins. A **nucleosome** is a single, wrapped DNA-histone complex. Multiple nucleosomes along the entire molecule of DNA appear like a beaded necklace, in which the string is the DNA and the beads are the associated histones. When a cell is in the process of division, the chromatin condenses into chromosomes, so that the DNA can be safely transported to the “daughter cells.” The **chromosome** is composed of DNA and proteins; it is the condensed form of chromatin. It is estimated that humans have almost 22,000 genes distributed on 46 chromosomes.

DNA Macrostructure

Strands of DNA are wrapped around supporting histones. These proteins are increasingly bundled and condensed into chromatin, which is packed tightly into chromosomes when the cell is ready to divide.



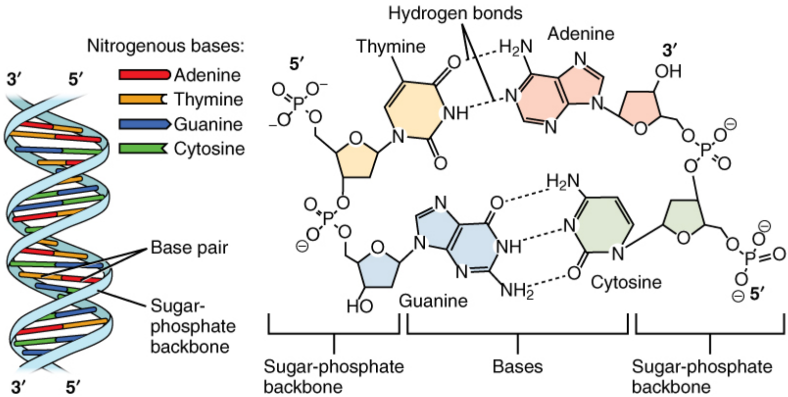
DNA Replication

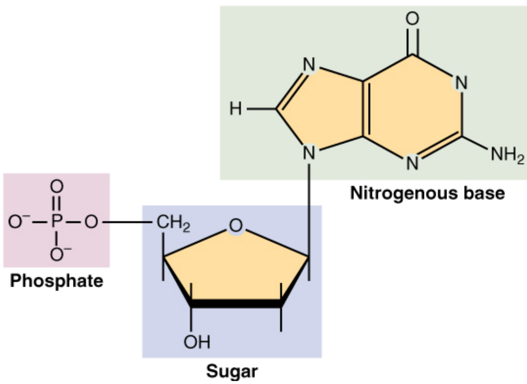
In order for an organism to grow, develop, and maintain its health, cells must reproduce themselves by dividing to produce two new daughter cells, each with the full complement of DNA as found in the original cell. Billions of new cells are produced in an adult human every day. Only very few cell types in the body do not divide, including nerve cells, skeletal muscle fibers, and cardiac muscle cells. The division time of different cell types varies. Epithelial cells of the skin and gastrointestinal lining, for instance, divide very frequently to replace those that are constantly being rubbed off of the surface by friction.

A DNA molecule is made of two strands that "complement" each other in the sense that the molecules that compose the strands fit together and bind to each other, creating a double-stranded molecule that looks much like a long, twisted ladder. Each side rail of the DNA ladder is composed of alternating sugar and phosphate groups ([link]). The two sides of the ladder are not identical, but are complementary. These two backbones are bonded to each other across pairs of protruding bases, each bonded pair forming one "rung," or cross member. The four DNA bases are adenine (A), thymine (T), cytosine (C), and guanine (G). Because of their shape and charge, the two bases that compose a pair always bond together. Adenine always binds with thymine, and cytosine always binds with guanine. The particular sequence of bases along the DNA molecule determines the genetic code. Therefore, if the two complementary strands of DNA were pulled apart, you could infer the order of the bases in one strand from the bases in the other, complementary strand. For example, if one strand has a region with the sequence AGTGCCT, then the sequence of the complementary strand would be TCACGGA.

Molecular Structure of DNA

The DNA double helix is composed of two complementary strands. The strands are bonded together via their nitrogenous base pairs using hydrogen bonds.



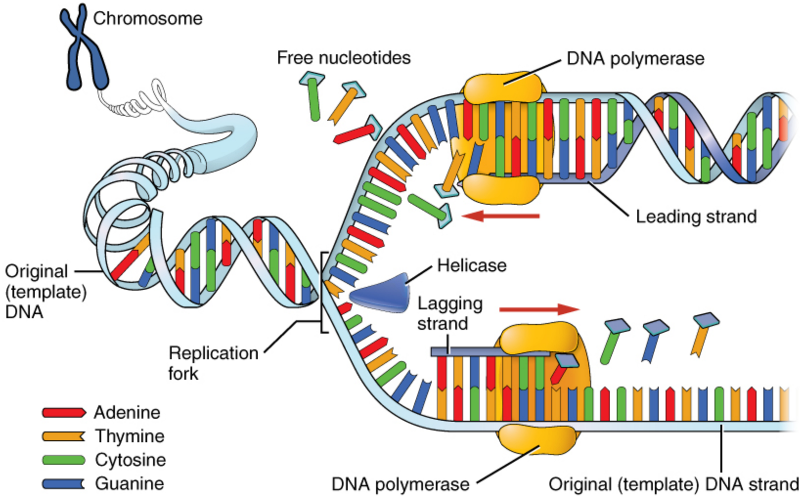


DNA replication is the copying of DNA that occurs before cell division can take place. After a great deal of debate and experimentation, the general method of DNA replication was deduced in 1958 by two scientists in California, Matthew Meselson and Franklin Stahl. This method is illustrated in [link] and described below.

DNA Replication

DNA replication faithfully duplicates the entire genome of the cell. During DNA replication, a number of different enzymes work together to pull apart the two strands so each strand can be used as

a template to synthesize new complementary strands. The two new daughter DNA molecules each contain one pre-existing strand and one newly synthesized strand. Thus, DNA replication is said to be “semiconservative.”



Stage 1: Initiation. The two complementary strands are separated, much like unzipping a zipper. Special enzymes, including **helicase**, untwist and separate the two strands of DNA.

Stage 2: Elongation. Each strand becomes a template along which a new complementary strand is built. **DNA polymerase** brings in the correct bases to complement the template strand, synthesizing a new strand base by base. A DNA polymerase is an enzyme that adds free nucleotides to the end of a chain of DNA, making a new double strand. This growing strand continues to be built until it has fully complemented the template strand.

Stage 3: Termination. Once the two original strands are bound to their own, finished, complementary strands, DNA replication is stopped and the two new identical DNA molecules are complete.

Each new DNA molecule contains one strand from the original molecule and one newly synthesized strand. The term for this mode of replication is "semiconservative," because half of the original DNA molecule is conserved in each new DNA molecule. This process continues until the cell's entire **genome**, the entire complement of an organism's DNA, is replicated. As you might imagine, it is very important that DNA replication take place precisely so that new cells in the body contain the exact same genetic material as their parent cells. Mistakes made during DNA replication, such as the accidental addition of an inappropriate nucleotide, have the potential to render a gene dysfunctional or useless. Fortunately, there are mechanisms in place to minimize such mistakes. A DNA proofreading process enlists the help of special enzymes that scan the newly synthesized molecule for mistakes and corrects them. Once the process of DNA replication is complete, the cell is ready to divide. You will explore the process of cell division later in the chapter.

Watch this video to learn about DNA replication. DNA replication proceeds simultaneously at several sites on the same molecule. What separates the base pair at the start of DNA replication?

Chapter Review

The nucleus is the command center of the cell, containing the genetic instructions for all of the materials a cell will make (and thus all of its functions it can perform). The nucleus is encased within a membrane of two interconnected lipid bilayers, side-by-side. This nuclear envelope is studded with protein-lined pores that allow materials to be trafficked into and out of the nucleus. The nucleus contains one or more nucleoli, which serve as sites for ribosome synthesis. The nucleus houses the genetic material of the cell: DNA. DNA is normally found as a loosely contained structure called chromatin within the nucleus, where it is wound up and associated with a variety

of histone proteins. When a cell is about to divide, the chromatin coils tightly and condenses to form chromosomes.

There is a pool of cells constantly dividing within your body. The result is billions of new cells being created each day. Before any cell is ready to divide, it must replicate its DNA so that each new daughter cell will receive an exact copy of the organism's genome. A variety of enzymes are enlisted during DNA replication. These enzymes unwind the DNA molecule, separate the two strands, and assist with the building of complementary strands along each parent strand. The original DNA strands serve as templates from which the nucleotide sequence of the new strands are determined and synthesized. When replication is completed, two identical DNA molecules exist. Each one contains one original strand and one newly synthesized complementary strand.

Interactive Link Questions

> Watch this video to learn about DNA replication. DNA replication proceeds simultaneously at several sites on the same molecule. What separates the base pair at the start of DNA replication?

an enzyme

Review Questions

The nucleus and mitochondria share which of the following features?

1. protein-lined membrane pores
2. a double cell membrane
3. the synthesis of ribosomes
4. the production of cellular energy

B

Which of the following structures could be found within the nucleolus?

1. chromatin
2. histones
3. ribosomes
4. nucleosomes

C

Which of the following sequences on a DNA molecule would be complementary to GCTTATAT?

1. TAGGCGCG
2. ATCCGCGC
3. CGAATATA
4. TGCCTCTC

C

Place the following structures in order from least to most complex organization: chromatin, nucleosome, DNA, chromosome

1. DNA, nucleosome, chromatin, chromosome
2. nucleosome, DNA, chromosome, chromatin
3. DNA, chromatin, nucleosome, chromosome
4. nucleosome, chromatin, DNA, chromosome

A

Which of the following is part of the elongation step of DNA synthesis?

1. pulling apart the two DNA strands
2. attaching complementary nucleotides to the template strand

3. untwisting the DNA helix
4. none of the above

B

Critical Thinking Questions

Explain in your own words why DNA replication is said to be “semiconservative”?

DNA replication is said to be semiconservative because, after replication is complete, one of the two parent DNA strands makes up half of each new DNA molecule. The other half is a newly synthesized strand. Therefore, half (“semi”) of each daughter DNA molecule is from the parent molecule and half is a new molecule.

Why is it important that DNA replication take place before cell division? What would happen if cell division of a body cell took place without DNA replication, or when DNA replication was incomplete?

During cell division, one cell divides to produce two new cells. In order for all of the cells in your body to maintain a full genome, each cell must replicate its DNA before it divides so that a full genome can be allotted to each of its offspring cells. If DNA replication did not take place fully, or at all, the offspring cells would be missing some or all of the genome. This could be disastrous if a cell was missing genes necessary for its function and health.

Glossary

chromatin
: substance consisting of DNA and associated proteins

chromosome
: condensed version of chromatin

DNA polymerase
: enzyme that functions in adding new nucleotides to a growing strand of DNA during DNA replication

DNA replication
: process of duplicating a molecule of DNA

genome
: entire complement of an organism’s DNA; found within virtually every cell

helicase
: enzyme that functions to separate the two DNA strands of a double helix during DNA replication

histone
: family of proteins that associate with DNA in the nucleus to form chromatin

nuclear envelope
: membrane that surrounds the nucleus; consisting of a double lipid-bilayer

nuclear pore
: one of the small, protein-lined openings found scattered throughout the nuclear envelope

nucleolus
: small region of the nucleus that functions in ribosome synthesis

nucleosome
: unit of chromatin consisting of a DNA strand wrapped around histone proteins

Cellular Differentiation

By the end of this section, you will be able to:

- Discuss how the generalized cells of a developing embryo or the stem cells of an adult organism become differentiated into specialized cells
- Distinguish between the categories of stem cells

How does a complex organism such as a human develop from a single cell—a fertilized egg—into the vast array of cell types such as nerve cells, muscle cells, and epithelial cells that characterize the adult? Throughout development and adulthood, the process of cellular differentiation leads cells to assume their final morphology and physiology. Differentiation is the process by which unspecialized cells become specialized to carry out distinct functions.

Stem Cells

A **stem cell** is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate.

The first embryonic cells that arise from the division

of the zygote are the ultimate stem cells; these stems cells are described as **totipotent** because they have the potential to differentiate into any of the cells needed to enable an organism to grow and develop.

The embryonic cells that develop from totipotent stem cells and are precursors to the fundamental tissue layers of the embryo are classified as pluripotent. A **pluripotent** stem cell is one that has the potential to differentiate into any type of human tissue but cannot support the full development of an organism. These cells then become slightly more specialized, and are referred to as multipotent cells.

A **multipotent** stem cell has the potential to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell.

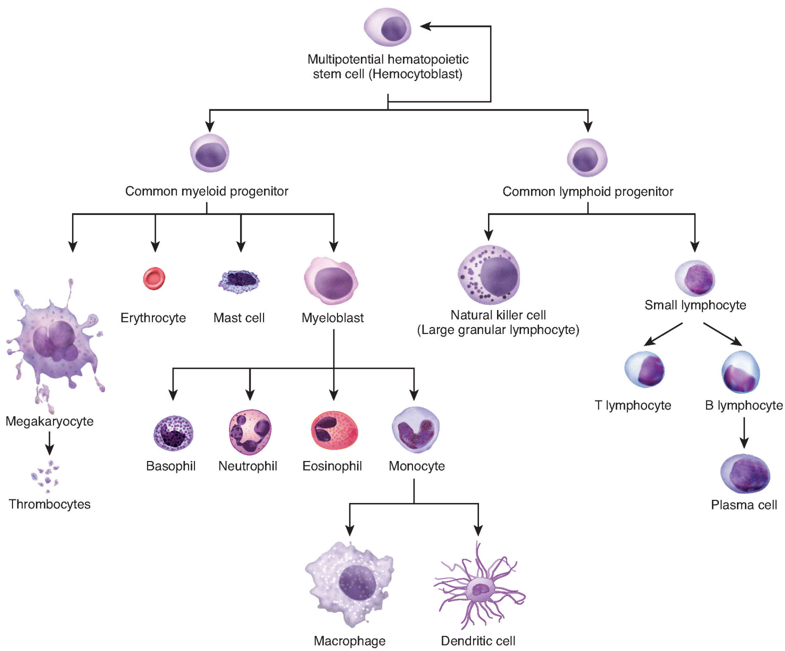
Finally, multipotent cells can become further specialized oligopotent cells. An **oligopotent** stem cell is limited to becoming one of a few different cell types. In contrast, a **unipotent** cell is fully specialized and can only reproduce to generate more of its own specific cell type.

Stem cells are unique in that they can also continually divide and regenerate new stem cells instead of further specializing. There are different stem cells present at different stages of a human's life. They include the embryonic stem cells of the

embryo, fetal stem cells of the fetus, and adult stem cells in the adult. One type of adult stem cell is the epithelial stem cell, which gives rise to the keratinocytes in the multiple layers of epithelial cells in the epidermis of skin. Adult bone marrow has three distinct types of stem cells: hematopoietic stem cells, which give rise to red blood cells, white blood cells, and platelets ([link]); endothelial stem cells, which give rise to the endothelial cell types that line blood and lymph vessels; and mesenchymal stem cells, which give rise to the different types of muscle cells.

Hematopoiesis

The process of hematopoiesis involves the differentiation of multipotent cells into blood and immune cells. The multipotent hematopoietic stem cells give rise to many different cell types, including the cells of the immune system and red blood cells.



Differentiation

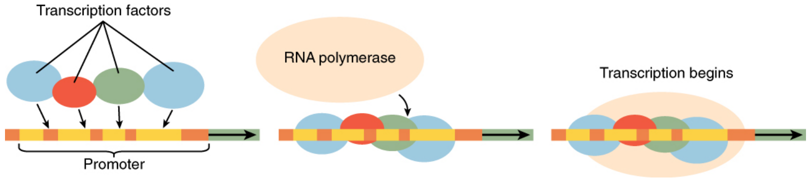
When a cell differentiates (becomes more specialized), it may undertake major changes in its size, shape, metabolic activity, and overall function. Because all cells in the body, beginning with the fertilized egg, contain the same DNA, how do the different cell types come to be so different? The answer is analogous to a movie script. The different actors in a movie all read from the same script, however, they are each only reading their own part of the script. Similarly, all cells contain the same full complement of DNA, but each type of cell only "reads" the portions of DNA that are relevant to its

own function. In biology, this is referred to as the unique genetic expression of each cell.

In order for a cell to differentiate into its specialized form and function, it need only manipulate those genes (and thus those proteins) that will be expressed, and not those that will remain silent. The primary mechanism by which genes are turned "on" or "off" is through transcription factors. A **transcription factor** is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription ([link]).

Transcription Factors Regulate Gene Expression

While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors are proteins that affect the binding of RNA polymerase to a particular gene on the DNA molecule.



Everyday Connection

Stem Cell Research

Stem cell research aims to find ways to use stem cells to regenerate and repair cellular damage. Over time, most adult cells undergo the wear and

tear of aging and lose their ability to divide and repair themselves. Stem cells do not display a particular morphology or function. Adult stem cells, which exist as a small subset of cells in most tissues, keep dividing and can differentiate into a number of specialized cells generally formed by that tissue. These cells enable the body to renew and repair body tissues.

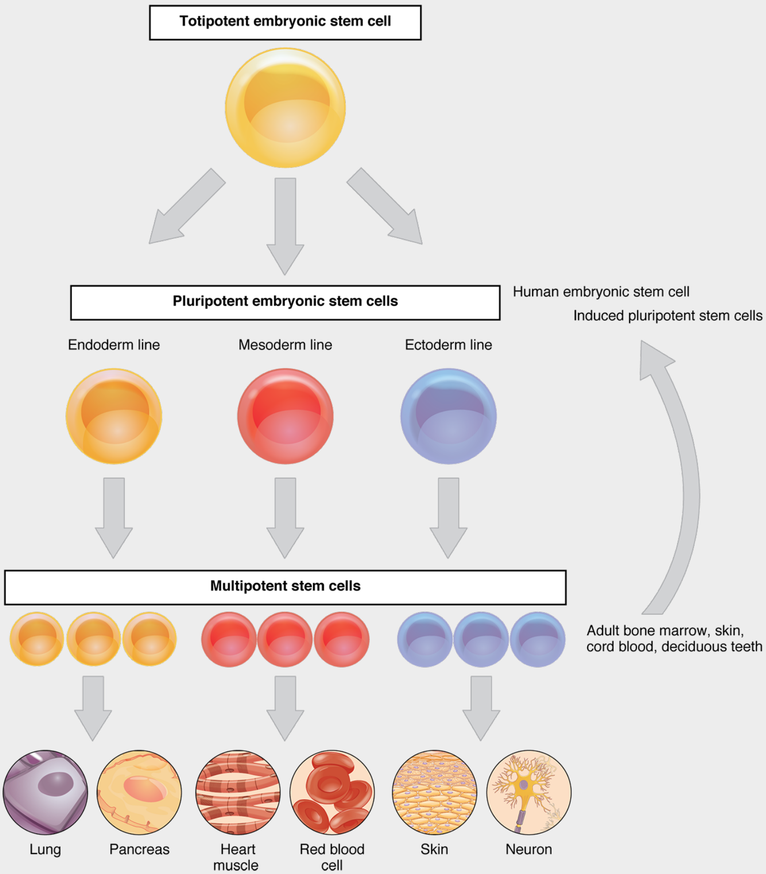
The mechanisms that induce a non-differentiated cell to become a specialized cell are poorly understood. In a laboratory setting, it is possible to induce stem cells to differentiate into specialized cells by changing the physical and chemical conditions of growth. Several sources of stem cells are used experimentally and are classified according to their origin and potential for differentiation. Human embryonic stem cells (hESCs) are extracted from embryos and are pluripotent. The adult stem cells that are present in many organs and differentiated tissues, such as bone marrow and skin, are multipotent, being limited in differentiation to the types of cells found in those tissues. The stem cells isolated from umbilical cord blood are also multipotent, as are cells from deciduous teeth (baby teeth). Researchers have recently developed induced pluripotent stem cells (iPSCs) from mouse and human adult stem cells. These cells are genetically reprogrammed multipotent adult cells that function like embryonic stem cells; they are capable of generating cells characteristic of all three germ

layers.

Because of their capacity to divide and differentiate into specialized cells, stem cells offer a potential treatment for diseases such as diabetes and heart disease ([link]). Cell-based therapy refers to treatment in which stem cells induced to differentiate in a growth dish are injected into a patient to repair damaged or destroyed cells or tissues. Many obstacles must be overcome for the application of cell-based therapy. Although embryonic stem cells have a nearly unlimited range of differentiation potential, they are seen as foreign by the patient's immune system and may trigger rejection. Also, the destruction of embryos to isolate embryonic stem cells raises considerable ethical and legal questions.

Stem Cells

The capacity of stem cells to differentiate into specialized cells make them potentially valuable in therapeutic applications designed to replace damaged cells of different body tissues.



In contrast, adult stem cells isolated from a patient are not seen as foreign by the body, but they have a limited range of differentiation. Some individuals bank the cord blood or deciduous teeth of their child, storing away those sources of stem cells for future use, should their child need it. Induced pluripotent stem cells are considered a promising advance in the field because using them avoids the legal, ethical, and immunological pitfalls of embryonic stem cells.

Chapter Review

One of the major areas of research in biology is that of how cells specialize to assume their unique structures and functions, since all cells essentially originate from a single fertilized egg. Cell differentiation is the process of cells becoming specialized as they body develops. A stem cell is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate. While all somatic cells contain the exact same genome, different cell types only express some of those genes at any given time. These differences in gene expression ultimately dictate a cell's unique morphological and physiological characteristics. The primary mechanism that determines which genes will be expressed and which ones will not is through the use of different transcription factor proteins, which bind to DNA and promote or hinder the transcription of different genes. Through the action of these transcription factors, cells specialize into one of hundreds of different cell types in the human body.

Review Questions

Arrange the following terms in order of increasing specialization: oligopotency, pleuripotency, unipotency, multipotency.

1. multipotency, pleuripotency, oligopotency, unipotency
2. pleuripotency, oligopotency, multipotency unipotency
3. oligopotency, pleuripotency, unipotency, multipotency
4. pleuripotency, multipotency, oligopotency, unipotency

D

Which type of stem cell gives rise to red and white blood cells?

1. endothelial
2. epithelial
3. hematopoietic
4. mesenchymal

C

What multipotent stem cells from children sometimes banked by parents?

1. fetal stem cells
2. embryonic stem cells
3. cells from the umbilical cord and from baby teeth
4. hematopoietic stem cells from red and white blood cells

C

Critical Thinking Questions

Explain how a transcription factor ultimately determines whether or not a protein will be present in a given cell?

Transcription factors bind to DNA and either promote or inhibit the transcription of a gene. If they promote the transcription of a particular gene, then that gene will be transcribed and the mRNA subsequently translated into protein. If gene transcription is inhibited, then there will be no way of synthesizing the gene’s corresponding protein.

Discuss two reasons why the therapeutic use of embryonic stem cells can present a problem.

Embryonic stem cells derive from human embryos, which are destroyed to obtain the cells. The destruction of human embryos is an ethical problem. And, the DNA in an embryonic stem cell would differ from the DNA of the person being treated, which could result in immune problems or rejected of tissue.

Glossary

multipotent
: describes the condition of being able to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell

oligopotent
: describes the condition of being more specialized than multipotency; the condition of being able to differentiate into one of a few possible cell types

pluripotent
: describes the condition of being able to differentiate into a large variety of cell types

stem cell
: cell that is oligo-, multi-, or pleuripotent that has the ability to produce additional stem cells rather than becoming further specialized

totipotent
: embryonic cells that have the ability to differentiate into any type of cell and organ in the body

transcription factor
: one of the proteins that regulate the transcription of genes

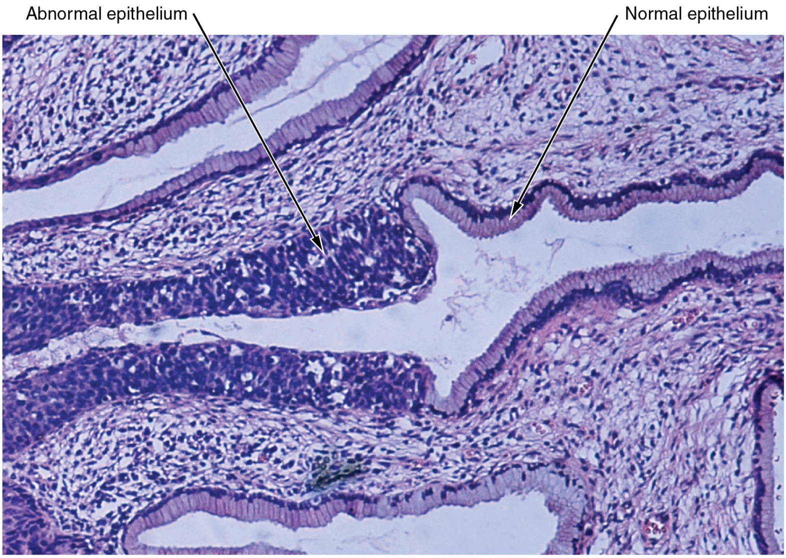
unipotent
: describes the condition of being committed to a single specialized cell type

Introduction

class="introduction"

Micrograph of Cervical Tissue

This figure is a view of the regular architecture of normal tissue contrasted with the irregular arrangement of cancerous cells. (credit: “Haymanj”/ Wikimedia Commons)



Chapter Objectives

After studying this chapter, you will be able to:

- Identify the main tissue types and discuss their roles in the human body
- Identify the four types of tissue membranes and the characteristics of each that make them functional

- Explain the functions of various epithelial tissues and how their forms enable their functions
- Explain the functions of various connective tissues and how their forms enable their functions
- Describe the characteristics of muscle tissue and how these enable function
- Discuss the characteristics of nervous tissue and how these enable information processing and control of muscular and glandular activities

The body contains at least 200 distinct cell types. These cells contain essentially the same internal structures yet they vary enormously in shape and function. The different types of cells are not randomly distributed throughout the body; rather they occur in organized layers, a level of organization referred to as tissue. The micrograph that opens this chapter shows the high degree of organization among different types of cells in the tissue of the cervix. You can also see how that organization breaks down when cancer takes over the regular mitotic functioning of a cell.

The variety in shape reflects the many different roles that cells fulfill in your body. The human body starts as a single cell at fertilization. As this

fertilized egg divides, it gives rise to trillions of cells, each built from the same blueprint, but organizing into tissues and becoming irreversibly committed to a developmental pathway.

Types of Tissues

By the end of this section, you will be able to:

- Identify the four main tissue types
- Discuss the functions of each tissue type
- Relate the structure of each tissue type to their function
- Discuss the embryonic origin of tissue
- Identify the three major germ layers
- Identify the main types of tissue membranes

The term **tissue** is used to describe a group of cells found together in the body. The cells within a tissue share a common embryonic origin. Microscopic observation reveals that the cells in a tissue share morphological features and are arranged in an orderly pattern that achieves the tissue's functions. From the evolutionary perspective, tissues appear in more complex organisms. For example, multicellular protists, ancient eukaryotes, do not have cells organized into tissues.

Although there are many types of cells in the human body, they are organized into four broad categories of tissues: epithelial, connective, muscle, and nervous. Each of these categories is characterized by specific functions that contribute to the overall health and maintenance of the body. A disruption of the structure is a sign of injury or disease. Such changes can be detected through **histology**, the microscopic study of tissue appearance,

organization, and function.

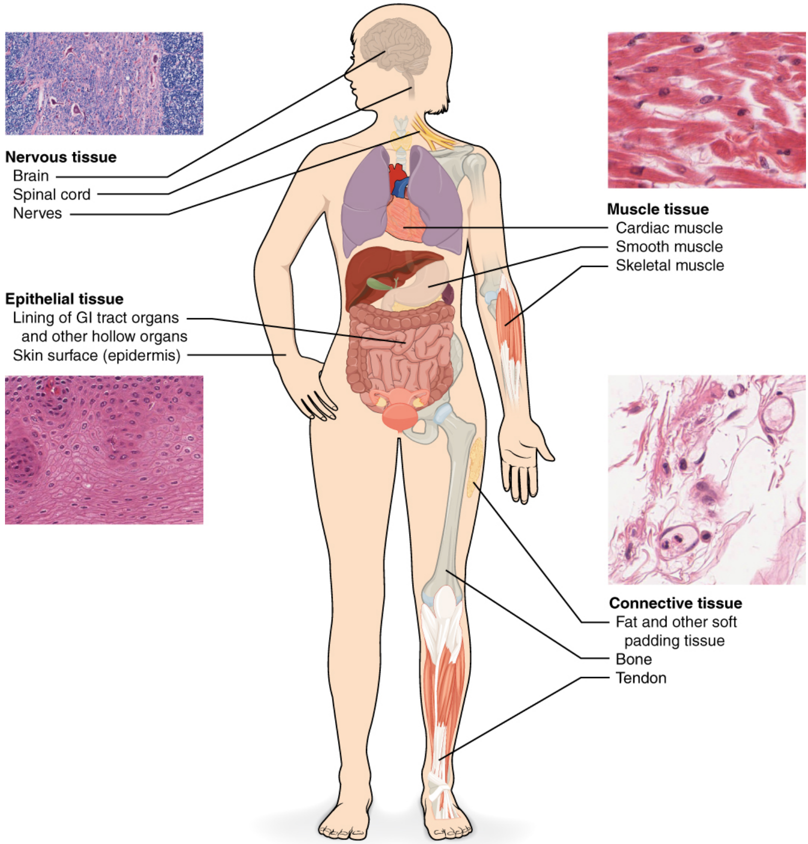
The Four Types of Tissues

Epithelial tissue, also referred to as epithelium, refers to the sheets of cells that cover exterior surfaces of the body, lines internal cavities and passageways, and forms certain glands. **Connective tissue**, as its name implies, binds the cells and organs of the body together and functions in the protection, support, and integration of all parts of the body. **Muscle tissue** is excitable, responding to stimulation and contracting to provide movement, and occurs as three major types: skeletal (voluntary) muscle, smooth muscle, and cardiac muscle in the heart. **Nervous tissue** is also excitable, allowing the propagation of electrochemical signals in the form of nerve impulses that communicate between different regions of the body ([link]).

The next level of organization is the organ, where several types of tissues come together to form a working unit. Just as knowing the structure and function of cells helps you in your study of tissues, knowledge of tissues will help you understand how organs function. The epithelial and connective tissues are discussed in detail in this chapter. Muscle and nervous tissues will be discussed only briefly in this chapter.

Four Types of Tissue: Body

The four types of tissues are exemplified in nervous tissue, stratified squamous epithelial tissue, cardiac muscle tissue, and connective tissue in small intestine. Clockwise from nervous tissue, LM × 872, LM × 282, LM × 460, LM × 800. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

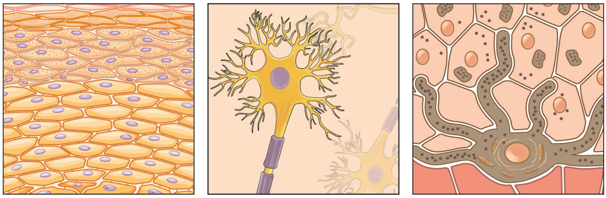
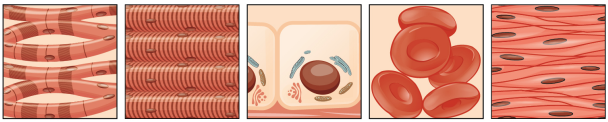
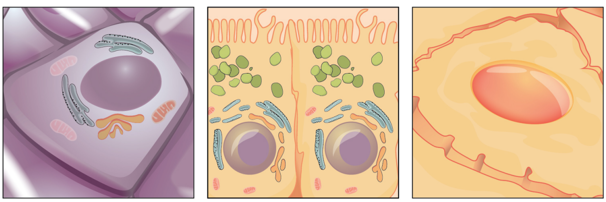


Embryonic Origin of Tissues

The zygote, or fertilized egg, is a single cell formed

by the fusion of an egg and sperm. After fertilization the zygote gives rise to rapid mitotic cycles, generating many cells to form the embryo. The first embryonic cells generated have the ability to differentiate into any type of cell in the body and, as such, are called **totipotent**, meaning each has the capacity to divide, differentiate, and develop into a new organism. As cell proliferation progresses, three major cell lineages are established within the embryo. As explained in a later chapter, each of these lineages of embryonic cells forms the distinct germ layers from which all the tissues and organs of the human body eventually form. Each germ layer is identified by its relative position: **ectoderm** (ecto- = “outer”), **mesoderm** (meso- = “middle”), and **endoderm** (endo- = “inner”). [link] shows the types of tissues and organs associated with the each of the three germ layers. Note that epithelial tissue originates in all three layers, whereas nervous tissue derives primarily from the ectoderm and muscle tissue from mesoderm.

Embryonic Origin of Tissues and Major Organs

Germ Layer	Gives rise to:
Ectoderm	Epidermis, glands on skin, some cranial bones, pituitary and adrenal medulla, the nervous system, the mouth between cheek and gums, the anus  Skin cells; Neurons; Pigment cell
Mesoderm	Connective tissues proper, bone, cartilage, blood, endothelium of blood vessels, muscle, synovial membranes, serous membranes lining body cavities, kidneys, lining of gonads  Cardiac muscle; Skeletal muscle; Tubule cell of kidney; Red blood cells; Smooth muscle
Endoderm	Lining of airways and digestive system except the mouth and distal part of digestive system (rectum and anal canal); glands (digestive glands, endocrine glands, adrenal cortex)  Lung cell; Thyroid cell; Pancreatic cell

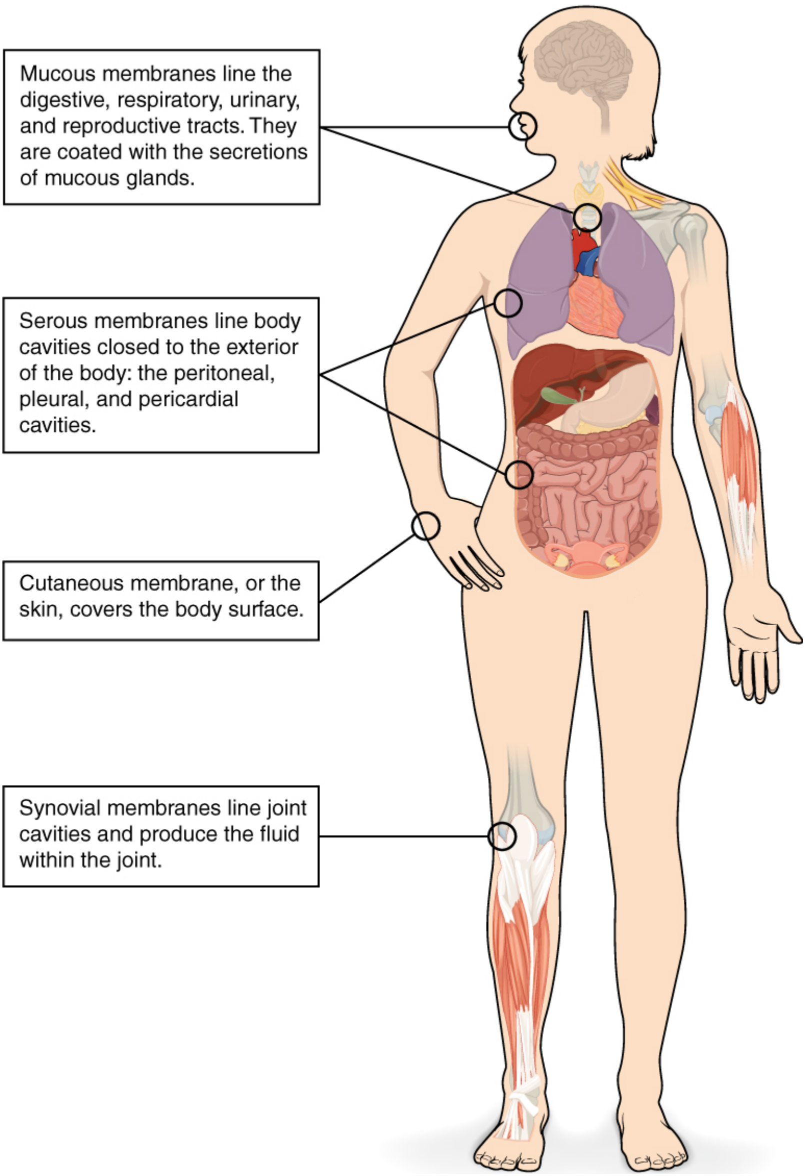
View this slideshow to learn more about stem cells. How do somatic stem cells differ from embryonic stem cells?

Tissue Membranes

A **tissue membrane** is a thin layer or sheet of cells that covers the outside of the body (for example, skin), the organs (for example, pericardium), internal passageways that lead to the exterior of the body (for example, abdominal mesenteries), and the lining of the moveable joint cavities. There are two basic types of tissue membranes: connective tissue and epithelial membranes ([link]).

Tissue Membranes

The two broad categories of tissue membranes in the body are (1) connective tissue membranes, which include synovial membranes, and (2) epithelial membranes, which include mucous membranes, serous membranes, and the cutaneous membrane, in other words, the skin.



Connective Tissue Membranes

The **connective tissue membrane** is formed solely from connective tissue. These membranes

encapsulate organs, such as the kidneys, and line our movable joints. A **synovial membrane** is a type of connective tissue membrane that lines the cavity of a freely movable joint. For example, synovial membranes surround the joints of the shoulder, elbow, and knee. Fibroblasts in the inner layer of the synovial membrane release hyaluronan into the joint cavity. The hyaluronan effectively traps available water to form the synovial fluid, a natural lubricant that enables the bones of a joint to move freely against one another without much friction. This synovial fluid readily exchanges water and nutrients with blood, as do all body fluids.

Epithelial Membranes

The **epithelial membrane** is composed of epithelium attached to a layer of connective tissue, for example, your skin. The **mucous membrane** is also a composite of connective and epithelial tissues. Sometimes called mucosae, these epithelial membranes line the body cavities and hollow passageways that open to the external environment, and include the digestive, respiratory, excretory, and reproductive tracts. Mucous, produced by the epithelial exocrine glands, covers the epithelial layer. The underlying connective tissue, called the **lamina propria** (literally “own layer”), help support the fragile epithelial layer.

A **serous membrane** is an epithelial membrane

composed of mesodermally derived epithelium called the mesothelium that is supported by connective tissue. These membranes line the coelomic cavities of the body, that is, those cavities that do not open to the outside, and they cover the organs located within those cavities. They are essentially membranous bags, with mesothelium lining the inside and connective tissue on the outside. Serous fluid secreted by the cells of the thin squamous mesothelium lubricates the membrane and reduces abrasion and friction between organs. Serous membranes are identified according locations. Three serous membranes line the thoracic cavity; the two pleura that cover the lungs and the pericardium that covers the heart. A fourth, the peritoneum, is the serous membrane in the abdominal cavity that covers abdominal organs and forms double sheets of mesenteries that suspend many of the digestive organs.

The skin is an epithelial membrane also called the **cutaneous membrane**. It is a stratified squamous epithelial membrane resting on top of connective tissue. The apical surface of this membrane is exposed to the external environment and is covered with dead, keratinized cells that help protect the body from desiccation and pathogens.

Chapter Review

The human body contains more than 200 types of cells that can all be classified into four types of tissues: epithelial, connective, muscle, and nervous. Epithelial tissues act as coverings controlling the movement of materials across the surface. Connective tissue integrates the various parts of the body and provides support and protection to organs. Muscle tissue allows the body to move. Nervous tissues propagate information.

The study of the shape and arrangement of cells in tissue is called histology. All cells and tissues in the body derive from three germ layers in the embryo: the ectoderm, mesoderm, and endoderm.

Different types of tissues form membranes that enclose organs, provide a friction-free interaction between organs, and keep organs together. Synovial membranes are connective tissue membranes that protect and line the joints. Epithelial membranes are formed from epithelial tissue attached to a layer of connective tissue. There are three types of epithelial membranes: mucous, which contain glands; serous, which secrete fluid; and cutaneous which makes up the skin.

Interactive Link Questions

View this slideshow to learn more about stem cells. How do somatic stem cells differ from embryonic stem cells?

Most somatic stem cells give rise to only a few cell types.

Review Questions

Which of the following is not a type of tissue?

1. muscle
2. nervous
3. embryonic
4. epithelial

C

The process by which a less specialized cell matures into a more specialized cell is called _____.

1. differentiation
2. maturation
3. modification

4. specialization

A

Differentiated cells in a developing embryo derive from ______.

1. endothelium, mesothelium, and epithelium
2. ectoderm, mesoderm, and endoderm
3. connective tissue, epithelial tissue, and muscle tissue
4. epidermis, mesoderm, and endothelium

B

Which of the following lines the body cavities exposed to the external environment?

1. mesothelium
2. lamina propria
3. mesenteries
4. mucosa

D

Critical Thinking Questions

Identify the four types of tissue in the body, and describe the major functions of each tissue.

The four types of tissue in the body are epithelial, connective, muscle, and nervous. Epithelial tissue is made of layers of cells that cover the surfaces of the body that come into contact with the exterior world, line internal cavities, and form glands. Connective tissue binds the cells and organs of the body together and performs many functions, especially in the protection, support, and integration of the body. Muscle tissue, which responds to stimulation and contracts to provide movement, is divided into three major types: skeletal (voluntary) muscles, smooth muscles, and the cardiac muscle in the heart. Nervous tissue allows the body to receive signals and transmit information as electric impulses from one region of the body to another.

The zygote is described as totipotent because it ultimately gives rise to all the cells in your body including the highly specialized cells of your nervous system. Describe this transition, discussing the steps and processes that lead to

these specialized cells.

The zygote divides into many cells. As these cells become specialized, they lose their ability to differentiate into all tissues. At first they form the three primary germ layers. Following the cells of the ectodermal germ layer, they too become more restricted in what they can form. Ultimately, some of these ectodermal cells become further restricted and differentiate in to nerve cells.

What is the function of synovial membranes?

Synovial membranes are a type of connective tissue membrane that supports mobility in joints. The membrane lines the joint cavity and contains fibroblasts that produce hyaluronan, which leads to the production of synovial fluid, a natural lubricant that enables the bones of a joint to move freely against one another.

Glossary

connective tissue
: type of tissue that serves to hold in place, connect, and integrate the body’s organs and systems

connective tissue membrane
: connective tissue that encapsulates organs and lines movable joints

cutaneous membrane
: skin; epithelial tissue made up of a stratified squamous epithelial cells that cover the outside of the body

ectoderm
: outermost embryonic germ layer from which the epidermis and the nervous tissue derive

endoderm
: innermost embryonic germ layer from which most of the digestive system and lower respiratory system derive

epithelial membrane
: epithelium attached to a layer of connective tissue

epithelial tissue
: type of tissue that serves primarily as a covering or lining of body parts, protecting the body; it also functions in absorption, transport, and secretion

histology
: microscopic study of tissue architecture, organization, and function

lamina propria
: areolar connective tissue underlying a mucous membrane

mesoderm
: middle embryonic germ layer from which connective tissue, muscle tissue, and some epithelial tissue derive

mucous membrane
: tissue membrane that is covered by protective mucous and lines tissue exposed to the outside environment

muscle tissue
: type of tissue that is capable of contracting and generating tension in response to stimulation; produces movement.

nervous tissue
: type of tissue that is capable of sending and receiving impulses through electrochemical signals.

serous membrane
: type of tissue membrane that lines body cavities and lubricates them with serous fluid

synovial membrane
: connective tissue membrane that lines the cavities of freely movable joints, producing synovial fluid for lubrication

tissue
: group of cells that are similar in form and perform related functions

tissue membrane
: thin layer or sheet of cells that covers the outside of the body, organs, and internal cavities

totipotent
: embryonic cells that have the ability to differentiate into any type of cell and organ in the body

Muscle Tissue and Motion

By the end of this section, you will be able to:

- Identify the three types of muscle tissue
- Compare and contrast the functions of each muscle tissue type
- Explain how muscle tissue can enable motion

Muscle tissue is characterized by properties that allow movement. Muscle cells are excitable; they respond to a stimulus. They are contractile, meaning they can shorten and generate a pulling force. When attached between two movable objects, in other words, bones, contractions of the muscles cause the bones to move. Some muscle movement is voluntary, which means it is under conscious control. For example, a person decides to open a book and read a chapter on anatomy. Other movements are involuntary, meaning they are not under conscious control, such as the contraction of your pupil in bright light. Muscle tissue is classified into three types according to structure and function: skeletal, cardiac, and smooth ([link]).

Comparison of Structure

and Properties of Muscle Tissue Types

Tissue	Histology	Function	Location
Skeletal	Long cylindrical fiber, striated, many peripherally located nuclei	Voluntary movement, produces heat, protects organs	Attached to bones and around entrance points to body (e.g., mouth, anus)
Cardiac	Short, branched, striated, single central nucleus	Contracts to pump blood	Heart
Smooth	Short, spindle-shaped, no evident striation, single nucleus in each fiber	Involuntary movement, moves food, involuntary control of respiration, moves secretions, regulates flow of blood in	Walls of major organs and passageways

arteries by contraction

Skeletal muscle is attached to bones and its contraction makes possible locomotion, facial expressions, posture, and other voluntary movements of the body. Forty percent of your body mass is made up of skeletal muscle. Skeletal muscles generate heat as a byproduct of their contraction and thus participate in thermal homeostasis. Shivering is an involuntary contraction of skeletal muscles in response to perceived lower than normal body temperature. The muscle cell, or **myocyte**, develops from myoblasts derived from the mesoderm. Myocytes and their numbers remain relatively constant throughout life. Skeletal muscle tissue is arranged in bundles surrounded by connective tissue. Under the light microscope, muscle cells appear striated with many nuclei squeezed along the membranes. The **striation** is due to the regular alternation of the contractile proteins actin and myosin, along with the structural proteins that couple the contractile proteins to connective tissues. The cells are multinucleated as a result of the fusion of the many myoblasts that fuse to form each long muscle fiber.

Cardiac muscle forms the contractile walls of the heart. The cells of cardiac muscle, known as cardiomyocytes, also appear striated under the microscope. Unlike skeletal muscle fibers,

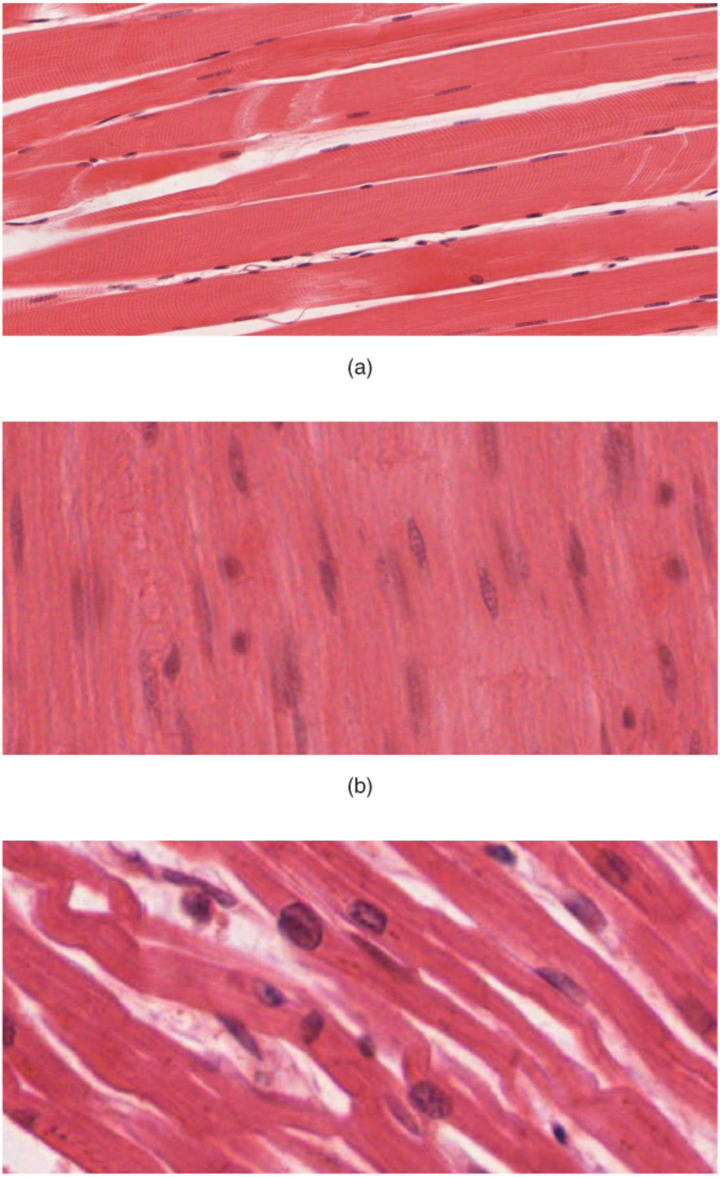
cardiomyocytes are single cells typically with a single centrally located nucleus. A principal characteristic of cardiomyocytes is that they contract on their own intrinsic rhythms without any external stimulation. Cardiomyocyte attach to one another with specialized cell junctions called intercalated discs. Intercalated discs have both anchoring junctions and gap junctions. Attached cells form long, branching cardiac muscle fibers that are, essentially, a mechanical and electrochemical syncytium allowing the cells to synchronize their actions. The cardiac muscle pumps blood through the body and is under involuntary control. The attachment junctions hold adjacent cells together across the dynamic pressures changes of the cardiac cycle.

Smooth muscle tissue contraction is responsible for involuntary movements in the internal organs. It forms the contractile component of the digestive, urinary, and reproductive systems as well as the airways and arteries. Each cell is spindle shaped with a single nucleus and no visible striations ([link]).

Muscle Tissue

(a) Skeletal muscle cells have prominent striation and nuclei on their periphery. (b) Smooth muscle cells have a single nucleus and no visible striations. (c) Cardiac muscle cells appear striated and have a single nucleus. From top, LM × 1600, LM × 1600, LM × 1600. (Micrographs provided by the Regents

of University of Michigan Medical School © 2012)



(a)

(b)

(c)

Watch this video to learn more about muscle tissue. In looking through a microscope how could you distinguish skeletal muscle tissue from smooth muscle?

Chapter Review

The three types of muscle cells are skeletal, cardiac, and smooth. Their morphologies match their specific functions in the body. Skeletal muscle is voluntary and responds to conscious stimuli. The cells are striated and multinucleated appearing as long, unbranched cylinders. Cardiac muscle is involuntary and found only in the heart. Each cell is striated with a single nucleus and they attach to one another to form long fibers. Cells are attached to one another at intercalated disks. The cells are interconnected physically and electrochemically to act as a syncytium. Cardiac muscle cells contract

autonomously and involuntarily. Smooth muscle is involuntary. Each cell is a spindle-shaped fiber and contains a single nucleus. No striations are evident because the actin and myosin filaments do not align in the cytoplasm.

Interactive Link Questions

Watch this video to learn more about muscle tissue. In looking through a microscope how could you distinguish skeletal muscle tissue from smooth muscle?

Skeletal muscle cells are striated.

Review Questions

Striations, cylindrical cells, and multiple nuclei are observed in ______.

1. skeletal muscle only
2. cardiac muscle only
3. smooth muscle only
4. skeletal and cardiac muscles

A

The cells of muscles, myocytes, develop from _____.

1. myoblasts
2. endoderm
3. fibrocytes
4. chondrocytes

A

Skeletal muscle is composed of very hard working cells. Which organelles do you expect to find in abundance in skeletal muscle cell?

1. nuclei
2. striations
3. golgi bodies
4. mitochondria

D

Critical Thinking Questions

You are watching cells in a dish spontaneously contract. They are all contracting at different rates; some fast, some slow. After a while, several cells link up and they begin contracting in synchrony. Discuss what is going on and what type of cells you are looking at.

The cells in the dish are cardiomyocytes, cardiac muscle cells. They have an intrinsic ability to contract. When they link up, they form intercalating discs that allow the cells to communicate with each other and begin contracting in synchrony.

Why does skeletal muscle look striated?

Under the light microscope, cells appear striated due to the arrangement of the contractile proteins actin and myosin.

Glossary

cardiac muscle
: heart muscle, under involuntary control, composed of striated cells that attach to form fibers, each cell contains a single nucleus, contracts autonomously

myocyte
: muscle cells

skeletal muscle
: usually attached to bone, under voluntary control, each cell is a fiber that is multinucleated and striated

smooth muscle
: under involuntary control, moves internal organs, cells contain a single nucleus, are spindle-shaped, and do not appear striated; each cell is a fiber

striation
: alignment of parallel actin and myosin filaments which form a banded pattern

Nervous Tissue Mediates Perception and Response

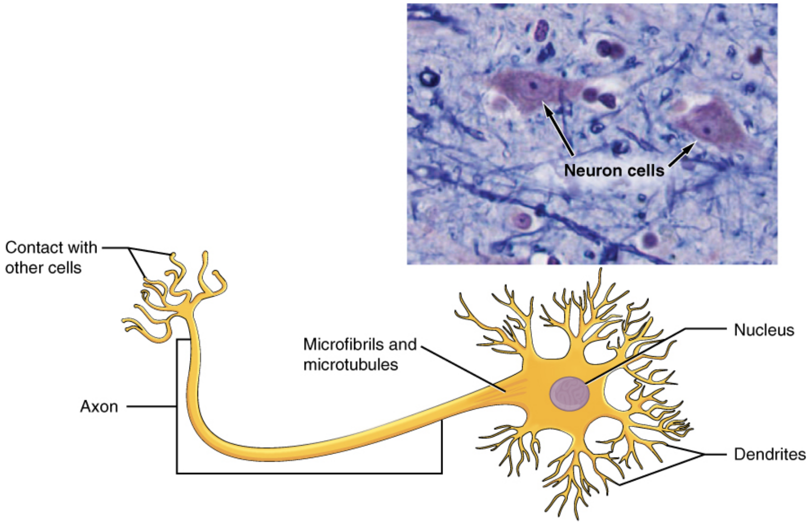
By the end of this section, you will be able to:

- Identify the classes of cells that make up nervous tissue
- Discuss how nervous tissue mediates perception and response

Nervous tissue is characterized as being excitable and capable of sending and receiving electrochemical signals that provide the body with information. Two main classes of cells make up nervous tissue: the **neuron** and **neuroglia** ([link]). Neurons propagate information via electrochemical impulses, called action potentials, which are biochemically linked to the release of chemical signals. Neuroglia play an essential role in supporting neurons and modulating their information propagation.

The Neuron

The cell body of a neuron, also called the soma, contains the nucleus and mitochondria. The dendrites transfer the nerve impulse to the soma. The axon carries the action potential away to another excitable cell. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Follow this link to learn more about nervous tissue. What are the main parts of a nerve cell?

Neurons display distinctive morphology, well suited to their role as conducting cells, with three main parts. The cell body includes most of the cytoplasm, the organelles, and the nucleus. Dendrites branch off

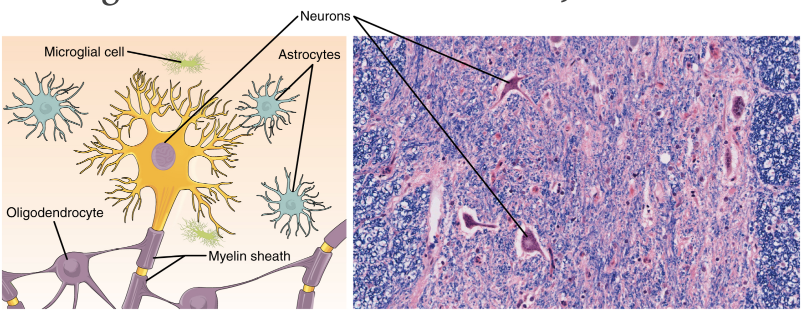
the cell body and appear as thin extensions. A long "tail," the axon, extends from the neuron body and can be wrapped in an insulating layer known as **myelin**, which is formed by accessory cells. The synapse is the gap between nerve cells, or between a nerve cell and its target, for example, a muscle or a gland, across which the impulse is transmitted by chemical compounds known as neurotransmitters. Neurons categorized as multipolar neurons have several dendrites and a single prominent axon. Bipolar neurons possess a single dendrite and axon with the cell body, while unipolar neurons have only a single process extending out from the cell body, which divides into a functional dendrite and into a functional axon. When a neuron is sufficiently stimulated, it generates an action potential that propagates down the axon towards the synapse. If enough neurotransmitters are released at the synapse to stimulate the next neuron or target, a response is generated.

The second class of neural cells comprises the neuroglia or glial cells, which have been characterized as having a simple support role. The word "glia" comes from the Greek word for glue. Recent research is shedding light on the more complex role of neuroglia in the function of the brain and nervous system. **Astrocyte** cells, named for their distinctive star shape, are abundant in the central nervous system. The astrocytes have many functions, including regulation of ion concentration

in the intercellular space, uptake and/or breakdown of some neurotransmitters, and formation of the blood-brain barrier, the membrane that separates the circulatory system from the brain. Microglia protect the nervous system against infection but are not nervous tissue because they are related to macrophages. **Oligodendrocyte** cells produce myelin in the central nervous system (brain and spinal cord) while the **Schwann cell** produces myelin in the peripheral nervous system ([link]).

Nervous Tissue

Nervous tissue is made up of neurons and neuroglia. The cells of nervous tissue are specialized to transmit and receive impulses. LM × 872. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Chapter Review

The most prominent cell of the nervous tissue, the neuron, is characterized mainly by its ability to receive stimuli and respond by generating an electrical signal, known as an action potential,

which can travel rapidly over great distances in the body. A typical neuron displays a distinctive morphology: a large cell body branches out into short extensions called dendrites, which receive chemical signals from other neurons, and a long tail called an axon, which relays signals away from the cell to other neurons, muscles, or glands. Many axons are wrapped by a myelin sheath, a lipid derivative that acts as an insulator and speeds up the transmission of the action potential. Other cells in the nervous tissue, the neuroglia, include the astrocytes, microglia, oligodendrocytes, and Schwann cells.

Interactive Link Questions

Follow this link to learn more about nervous tissue. What are the main parts of a nerve cell?

Dendrites, cell body, and the axon.

Review Questions

The cells responsible for the transmission of the

nerve impulse are _____.

1. neurons
2. oligodendrocytes
3. astrocytes
4. microglia

A

The nerve impulse travels down a(n) _____, away from the cell body.

1. dendrite
2. axon
3. microglia
4. collagen fiber

B

Which of the following central nervous system cells regulate ions, regulate the uptake and/or breakdown of some neurotransmitters, and contribute to the formation of the blood-brain barrier?

1. microglia
2. neuroglia
3. oligodendrocytes

4. astrocytes

D

Critical Thinking Questions

Which morphological adaptations of neurons make them suitable for the transmission of nerve impulse?

Neurons are well suited for the transmission of nerve impulses because short extensions, dendrites, receive impulses from other neurons, while a long tail extension, an axon, carries electrical impulses away from the cell to other neurons.

What are the functions of astrocytes?

Astrocytes regulate ions and uptake and/or breakdown of some neurotransmitters and contribute to the formation of the blood-brain-barrier.

References

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Glossary

astrocyte
: star-shaped cell in the central nervous system that regulates ions and uptake and/or breakdown of some neurotransmitters and contributes to the formation of the blood-brain barrier

myelin
: layer of lipid inside some neuroglial cells that wraps around the axons of some neurons

neuroglia
: supportive neural cells

neuron
: excitable neural cell that transfer nerve

impulses

oligodendrocyte
neuroglial cell that produces myelin in the brain

Schwann cell
neuroglial cell that produces myelin in the peripheral nervous system

Tissue Injury and Aging

By the end of this section, you will be able to:

- Identify the cardinal signs of inflammation
- List the body's response to tissue injury
- Explain the process of tissue repair
- Discuss the progressive impact of aging on tissue
- Describe cancerous mutations' effect on tissue

Tissues of all types are vulnerable to injury and, inevitably, aging. In the former case, understanding how tissues respond to damage can guide strategies to aid repair. In the latter case, understanding the impact of aging can help in the search for ways to diminish its effects.

Tissue Injury and Repair

Inflammation is the standard, initial response of the body to injury. Whether biological, chemical, physical, or radiation burns, all injuries lead to the same sequence of physiological events. Inflammation limits the extent of injury, partially or fully eliminates the cause of injury, and initiates repair and regeneration of damaged tissue. **Necrosis**, or accidental cell death, causes inflammation. **Apoptosis** is programmed cell death, a normal step-by-step process that destroys cells no

longer needed by the body. By mechanisms still under investigation, apoptosis does not initiate the inflammatory response. Acute inflammation resolves over time by the healing of tissue. If inflammation persists, it becomes chronic and leads to diseased conditions. Arthritis and tuberculosis are examples of chronic inflammation. The suffix “-itis” denotes inflammation of a specific organ or type, for example, peritonitis is the inflammation of the peritoneum, and meningitis refers to the inflammation of the meninges, the tough membranes that surround the central nervous system

The four cardinal signs of inflammation—redness, swelling, pain, and local heat—were first recorded in antiquity. Cornelius Celsus is credited with documenting these signs during the days of the Roman Empire, as early as the first century AD. A fifth sign, loss of function, may also accompany inflammation.

Upon tissue injury, damaged cells release inflammatory chemical signals that evoke local **vasodilation**, the widening of the blood vessels. Increased blood flow results in apparent redness and heat. In response to injury, mast cells present in tissue degranulate, releasing the potent vasodilator **histamine**. Increased blood flow and inflammatory mediators recruit white blood cells to the site of inflammation. The endothelium lining the local

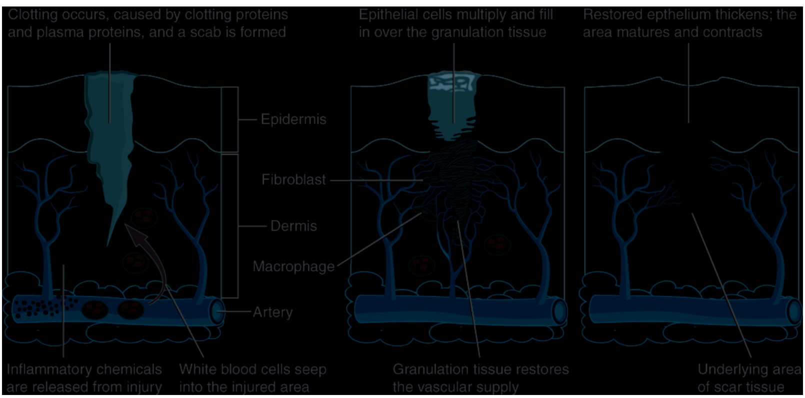
blood vessel becomes "leaky" under the influence of histamine and other inflammatory mediators allowing neutrophils, macrophages, and fluid to move from the blood into the interstitial tissue spaces. The excess liquid in tissue causes swelling, more properly called edema. The swollen tissues squeezing pain receptors cause the sensation of pain. Prostaglandins released from injured cells also activate pain neurons. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain because they inhibit the synthesis of prostaglandins. High levels of NSAIDs reduce inflammation. Antihistamines decrease allergies by blocking histamine receptors and as a result the histamine response.

After containment of an injury, the tissue repair phase starts with removal of toxins and waste products. **Clotting** (coagulation) reduces blood loss from damaged blood vessels and forms a network of fibrin proteins that trap blood cells and bind the edges of the wound together. A scab forms when the clot dries, reducing the risk of infection. Sometimes a mixture of dead leukocytes and fluid called pus accumulates in the wound. As healing progresses, fibroblasts from the surrounding connective tissues replace the collagen and extracellular material lost by the injury. Angiogenesis, the growth of new blood vessels, results in vascularization of the new tissue known as granulation tissue. The clot retracts pulling the edges of the wound together, and it

slowly dissolves as the tissue is repaired. When a large amount of granulation tissue forms and capillaries disappear, a pale scar is often visible in the healed area. A **primary union** describes the healing of a wound where the edges are close together. When there is a gaping wound, it takes longer to refill the area with cells and collagen. The process called **secondary union** occurs as the edges of the wound are pulled together by what is called **wound contraction**. When a wound is more than one quarter of an inch deep, sutures (stitches) are recommended to promote a primary union and avoid the formation of a disfiguring scar. Regeneration is the addition of new cells of the same type as the ones that were injured ([link]).

Tissue Healing

During wound repair, collagen fibers are laid down randomly by fibroblasts that move into repair the area.



Watch this video to see a hand heal. Over what period of time do you think these images were taken?

Tissue and Aging

According to poet Ralph Waldo Emerson, “The surest poison is time.” In fact, biology confirms that many functions of the body decline with age. All the cells, tissues, and organs are affected by senescence, with noticeable variability between individuals owing to different genetic makeup and lifestyles. The outward signs of aging are easily recognizable. The skin and other tissues become thinner and drier, reducing their elasticity, contributing to wrinkles and high blood pressure. Hair turns gray because follicles produce less melanin, the brown pigment of hair and the iris of the eye. The face looks flabby because elastic and collagen fibers decrease in connective tissue and muscle tone is lost. Glasses and hearing aids may become parts of life as the

senses slowly deteriorate, all due to reduced elasticity. Overall height decreases as the bones lose calcium and other minerals. With age, fluid decreases in the fibrous cartilage disks intercalated between the vertebrae in the spine. Joints lose cartilage and stiffen. Many tissues, including those in muscles, lose mass through a process called **atrophy**. Lumps and rigidity become more widespread. As a consequence, the passageways, blood vessels, and airways become more rigid. The brain and spinal cord lose mass. Nerves do not transmit impulses with the same speed and frequency as in the past. Some loss of thought clarity and memory can accompany aging. More severe problems are not necessarily associated with the aging process and may be symptoms of underlying illness.

As exterior signs of aging increase, so do the interior signs, which are not as noticeable. The incidence of heart diseases, respiratory syndromes, and type 2 diabetes increases with age, though these are not necessarily age-dependent effects. Wound healing is slower in the elderly, accompanied by a higher frequency of infection as the capacity of the immune system to fend off pathogen declines.

Aging is also apparent at the cellular level because all cells experience changes with aging. Telomeres, regions of the chromosomes necessary for cell division, shorten each time cells divide. As they do,

cells are less able to divide and regenerate. Because of alterations in cell membranes, transport of oxygen and nutrients into the cell and removal of carbon dioxide and waste products from the cell are not as efficient in the elderly. Cells may begin to function abnormally, which may lead to diseases associated with aging, including arthritis, memory issues, and some cancers.

The progressive impact of aging on the body varies considerably among individuals, but Studies indicate, however, that exercise and healthy lifestyle choices can slow down the deterioration of the body that comes with old age.

Homeostatic Imbalances

Tissues and Cancer

Cancer is a generic term for many diseases in which cells escape regulatory signals. Uncontrolled growth, invasion into adjacent tissues, and colonization of other organs, if not treated early enough, are its hallmarks. Health suffers when tumors “rob” blood supply from the “normal” organs.

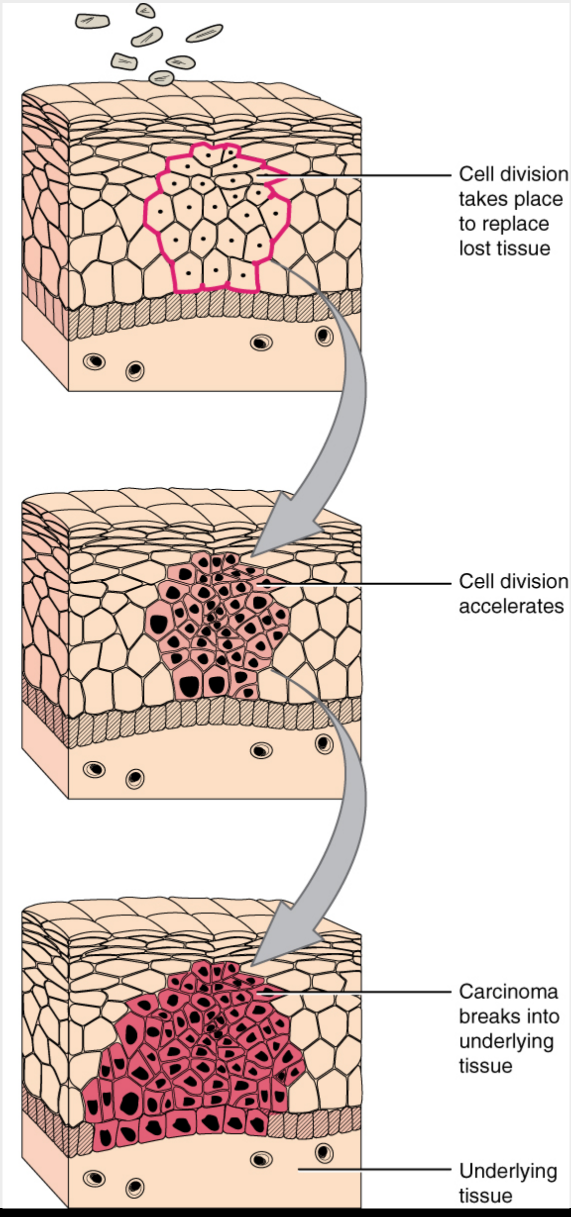
A mutation is defined as a permanent change in the DNA of a cell. Epigenetic modifications, changes that do not affect the code of the DNA but alter how the DNA is decoded, are also known to generate abnormal cells. Alterations in the genetic

material may be caused by environmental agents, infectious agents, or errors in the replication of DNA that accumulate with age. Many mutations do not cause any noticeable change in the functions of a cell. However, if the modification affects key proteins that have an impact on the cell's ability to proliferate in an orderly fashion, the cell starts to divide abnormally. As changes in cells accumulate, they lose their ability to form regular tissues. A tumor, a mass of cells displaying abnormal architecture, forms in the tissue. Many tumors are benign, meaning they do not metastasize nor cause disease. A tumor becomes malignant, or cancerous, when it breaches the confines of its tissue, promotes angiogenesis, attracts the growth of capillaries, and metastasizes to other organs ([link]). The specific names of cancers reflect the tissue of origin. Cancers derived from epithelial cells are referred to as carcinomas. Cancer in myeloid tissue or blood cells form myelomas. Leukemias are cancers of white blood cells, whereas sarcomas derive from connective tissue. Cells in tumors differ both in structure and function. Some cells, called cancer stem cells, appear to be a subtype of cell responsible for uncontrolled growth. Recent research shows that contrary to what was previously assumed, tumors are not disorganized masses of cells, but have their own structures.

Development of Cancer

Note the change in cell size, nucleus size, and

organization in the tissue.



Watch this video to learn more about tumors. What is a tumor?

Cancer treatments vary depending on the disease's type and stage. Traditional approaches, including surgery, radiation, chemotherapy, and hormonal therapy, aim to remove or kill rapidly dividing cancer cells, but these strategies have their limitations. Depending on a tumor's location, for example, cancer surgeons may be unable to remove it. Radiation and chemotherapy are difficult, and it is often impossible to target only the cancer cells. The treatments inevitably destroy healthy tissue as well. To address this, researchers are working on pharmaceuticals that can target specific proteins implicated in cancer-associated molecular pathways.

Chapter Review

Inflammation is the classic response of the body to

injury and follows a common sequence of events. The area is red, feels warm to the touch, swells, and is painful. Injured cells, mast cells, and resident macrophages release chemical signals that cause vasodilation and fluid leakage in the surrounding tissue. The repair phase includes blood clotting, followed by regeneration of tissue as fibroblasts deposit collagen. Some tissues regenerate more readily than others. Epithelial and connective tissues replace damaged or dead cells from a supply of adult stem cells. Muscle and nervous tissues undergo either slow regeneration or do not repair at all.

Age affects all the tissues and organs of the body. Damaged cells do not regenerate as rapidly as in younger people. Perception of sensation and effectiveness of response are lost in the nervous system. Muscles atrophy, and bones lose mass and become brittle. Collagen decreases in some connective tissue, and joints stiffen.

Interactive Link Questions

Watch this video to see a hand heal. Over what period of time do you think these images were taken?

Approximately one month.

Watch this video to learn more about tumors. What is a tumor?

A mass of cancer cells that continue to grow and divide.

Review Questions

Which of the following processes is not a cardinal sign of inflammation?

1. redness
2. heat
3. fever
4. swelling

C

When a mast cell reacts to an irritation, which of the following chemicals does it release?

1. collagen
2. histamine
3. hyaluronic acid

4. meylin

B

Atrophy refers to ______.

1. loss of elasticity
2. loss of mass
3. loss of rigidity
4. loss of permeability

B

Individuals can slow the rate of aging by modifying all of these lifestyle aspects except for ______.

1. diet
2. exercise
3. genetic factors
4. stress

C

Critical Thinking Questions

Why is it important to watch for increased redness, swelling and pain after a cut or abrasion has been cleaned and bandaged?

These symptoms would indicate that infection is present.

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) that inhibits the formation of blood clots and is taken regularly by individuals with a heart condition. Steroids such as cortisol are used to control some autoimmune diseases and severe arthritis by down-regulating the inflammatory response. After reading the role of inflammation in the body's response to infection, can you predict an undesirable consequence of taking anti-inflammatory drugs on a regular basis?

Since NSAIDs or other anti-inflammatory drugs inhibit the formation of blood clots, regular and prolonged use of these drugs may promote internal bleeding, such as bleeding in the stomach. Excessive levels of cortisol would suppress inflammation, which could slow the wound healing process.

As an individual ages, a constellation of symptoms begins the decline to the point where an individual’s functioning is compromised. Identify and discuss two factors that have a role in factors leading to the compromised situation.

The genetic makeup and the lifestyle of each individual are factors which determine the degree of decline in cells, tissues, and organs as an individual ages.

Discuss changes that occur in cells as a person ages.

All cells experience changes with aging. They become larger, and many cannot divide and regenerate. Because of alterations in cell membranes, transport of oxygen and nutrients into the cell and removal of carbon dioxide and waste products are not as efficient in the elderly. Cells lose their ability to function, or they begin to function abnormally, leading to disease and cancer.

References

Emerson, RW. Old age. Atlantic. 1862 [cited 2012

Dec 4]; 9(51):134–140.

Glossary

apoptosis
: programmed cell death

atrophy
: loss of mass and function

clotting
: also called coagulation; complex process by which blood components form a plug to stop bleeding

histamine
: chemical compound released by mast cells in response to injury that causes vasodilation and endothelium permeability

inflammation
: response of tissue to injury

necrosis
: accidental death of cells and tissues

primary union
: condition of a wound where the wound edges are close enough to be brought together and fastened if necessary, allowing quicker and more thorough healing

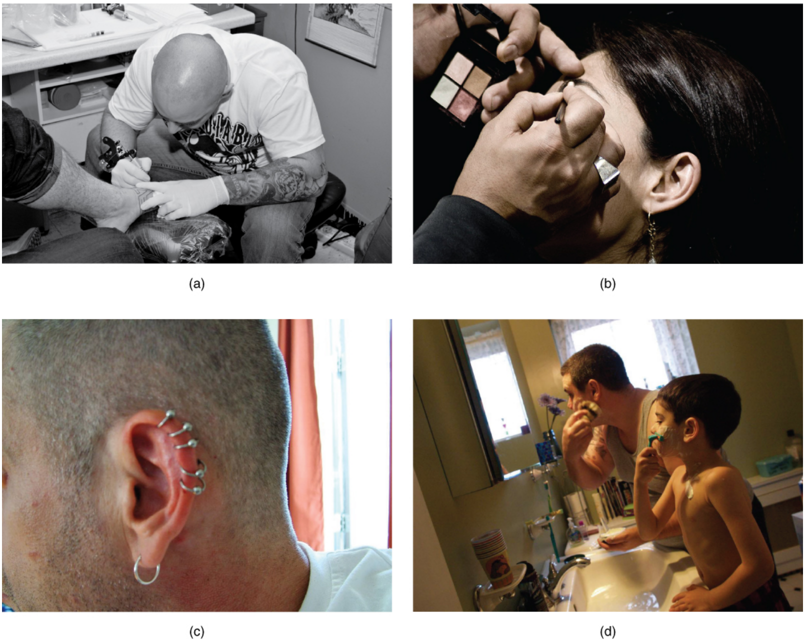
secondary union
: wound healing facilitated by wound contraction

vasodilation
: widening of blood vessels

wound contraction
: process whereby the borders of a wound are physically drawn together

Introduction

class="introduction" Your skin is a vital part of your life and appearance (a–d). Some people choose to embellish it with tattoos (a), makeup (b), and even piercings (c). (credit a: Steve Teo; credit b: “spaceodissey”/flickr; credit c: Mark/flickr; credit d: Lisa Schaffer)



Chapter Objectives

After studying the chapter, you will be able to:

- Describe the integumentary system and the role it plays in homeostasis
- Describe the layers of the skin and the

functions of each layer
- Describe the accessory structures of the skin and the functions of each
- Describe the changes that occur in the integumentary system during the aging process
- Discuss several common diseases, disorders, and injuries that affect the integumentary system
- Explain treatments for some common diseases, disorders, and injuries of the integumentary system

What do you think when you look at your skin in the mirror? Do you think about covering it with makeup, adding a tattoo, or maybe a body piercing? Or do you think about the fact that the skin belongs to one of the body's most essential and dynamic systems: the integumentary system? The integumentary system refers to the skin and its accessory structures, and it is responsible for much more than simply lending to your outward appearance. In the adult human body, the skin makes up about 16 percent of body weight and covers an area of 1.5 to 2 m^2. In fact, the skin and accessory structures are the largest organ system in the human body. As such, the skin protects your inner organs and it is in need of daily care and protection to maintain its health. This chapter will

introduce the structure and functions of the integumentary system, as well as some of the diseases, disorders, and injuries that can affect this system.

Layers of the Skin

By the end of this section, you will be able to:

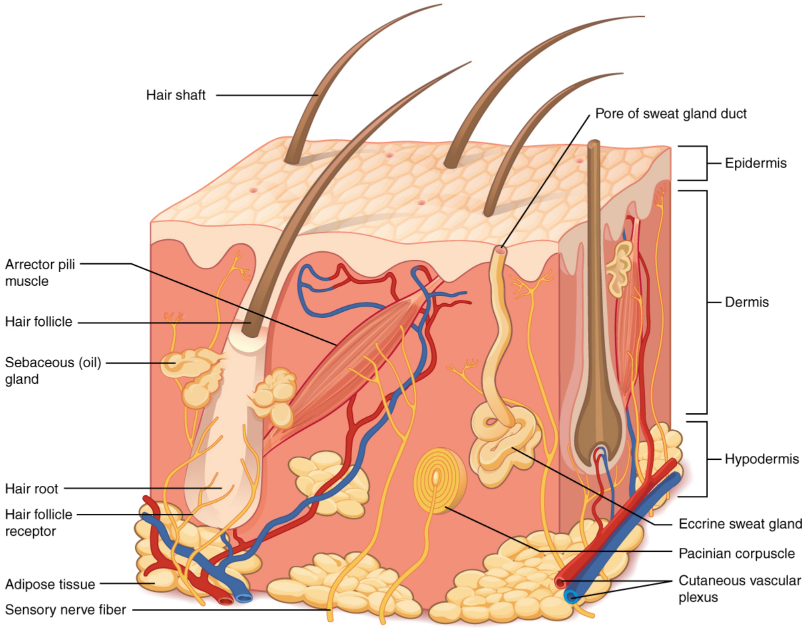
- Identify the components of the integumentary system
- Describe the layers of the skin and the functions of each layer
- Identify and describe the hypodermis and deep fascia
- Describe the role of keratinocytes and their life cycle
- Describe the role of melanocytes in skin pigmentation

Although you may not typically think of the skin as an organ, it is in fact made of tissues that work together as a single structure to perform unique and critical functions. The skin and its accessory structures make up the **integumentary system**, which provides the body with overall protection. The skin is made of multiple layers of cells and tissues, which are held to underlying structures by connective tissue ([link]). The deeper layer of skin is well vascularized (has numerous blood vessels). It also has numerous sensory, and autonomic and sympathetic nerve fibers ensuring communication to and from the brain.

Layers of Skin

The skin is composed of two main layers: the epidermis, made of closely packed epithelial cells, and the dermis, made of dense, irregular connective

tissue that houses blood vessels, hair follicles, sweat glands, and other structures. Beneath the dermis lies the hypodermis, which is composed mainly of loose connective and fatty tissues.



The skin consists of two main layers and a closely associated layer. View this animation to learn more

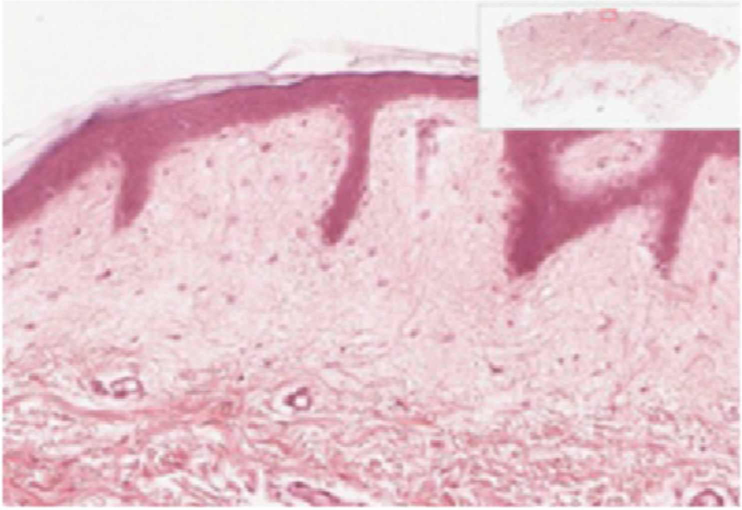
about layers of the skin. What are the basic functions of each of these layers?

The Epidermis

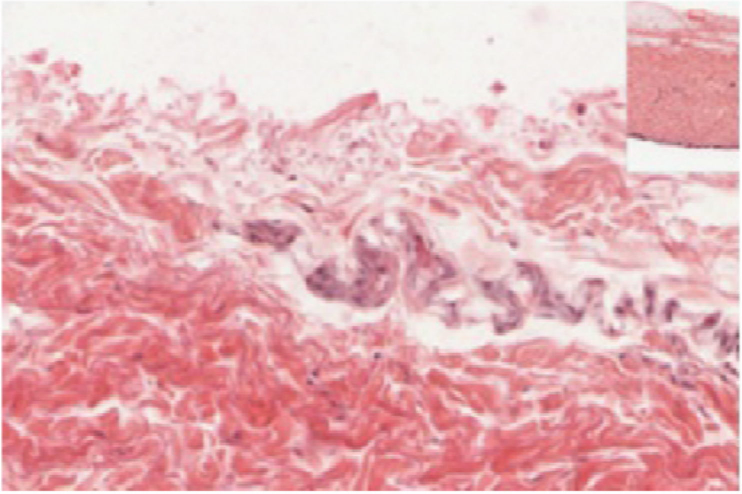
The **epidermis** is composed of keratinized, stratified squamous epithelium. It is made of four or five layers of epithelial cells, depending on its location in the body. It does not have any blood vessels within it (i.e., it is avascular). Skin that has four layers of cells is referred to as “thin skin.” From deep to superficial, these layers are the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum. Most of the skin can be classified as thin skin. “Thick skin” is found only on the palms of the hands and the soles of the feet. It has a fifth layer, called the stratum lucidum, located between the stratum corneum and the stratum granulosum ([link]).

Thin Skin versus Thick Skin

These slides show cross-sections of the epidermis and dermis of (a) thin and (b) thick skin. Note the significant difference in the thickness of the epithelial layer of the thick skin. From top, LM × 40, LM × 40. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)



(a)



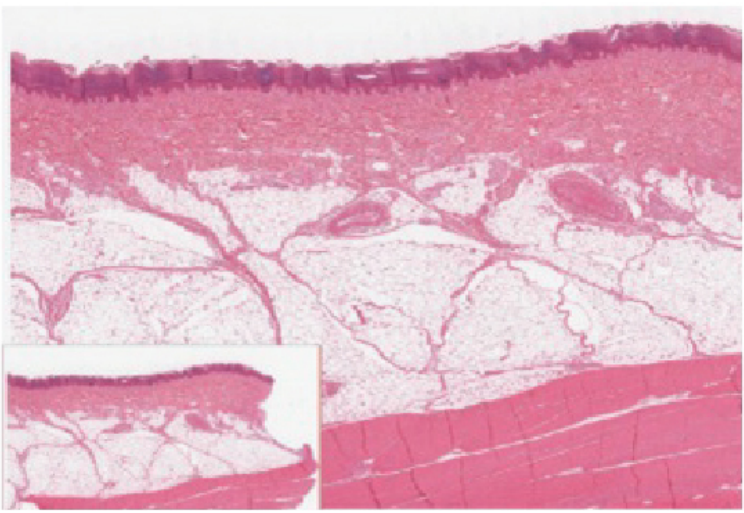
(b)

The cells in all of the layers except the stratum basale are called keratinocytes. A **keratinocyte** is a cell that manufactures and stores the protein keratin. **Keratin** is an intracellular fibrous protein that gives hair, nails, and skin their hardness and

water-resistant properties. The keratinocytes in the stratum corneum are dead and regularly slough away, being replaced by cells from the deeper layers ([link]).

Epidermis

The epidermis is epithelium composed of multiple layers of cells. The basal layer consists of cuboidal cells, whereas the outer layers are squamous, keratinized cells, so the whole epithelium is often described as being keratinized stratified squamous epithelium. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail. If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

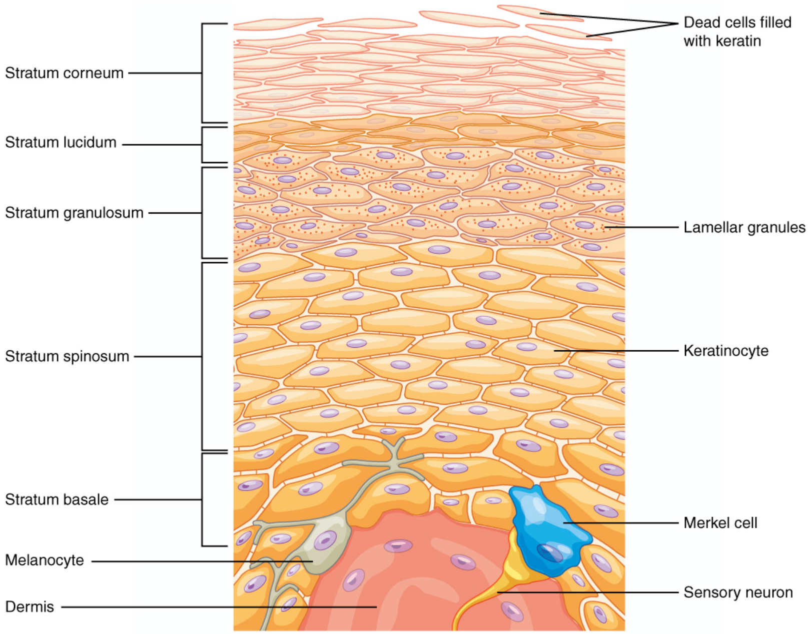
Stratum Basale

The **stratum basale** (also called the stratum germinativum) is the deepest epidermal layer and attaches the epidermis to the basal lamina, below which lie the layers of the dermis. The cells in the stratum basale bond to the dermis via intertwining collagen fibers, referred to as the basement membrane. A finger-like projection, or fold, known as the **dermal papilla** (plural = dermal papillae) is found in the superficial portion of the dermis. Dermal papillae increase the strength of the connection between the epidermis and dermis; the greater the folding, the stronger the connections made ([link]).

Layers of the Epidermis

The epidermis of thick skin has five layers: stratum basale, stratum spinosum, stratum granulosum,

stratum lucidum, and stratum corneum.



The stratum basale is a single layer of cells primarily made of basal cells. A **basal cell** is a cuboidal-shaped stem cell that is a precursor of the keratinocytes of the epidermis. All of the keratinocytes are produced from this single layer of cells, which are constantly going through mitosis to produce new cells. As new cells are formed, the existing cells are pushed superficially away from the stratum basale. Two other cell types are found dispersed among the basal cells in the stratum basale. The first is a **Merkel cell**, which functions as a receptor and is responsible for stimulating sensory nerves that the brain perceives as touch. These cells are especially abundant on the surfaces of the hands and feet. The second is a **melanocyte**, a cell that

produces the pigment melanin. **Melanin** gives hair and skin its color, and also helps protect the living cells of the epidermis from ultraviolet (UV) radiation damage.

In a growing fetus, fingerprints form where the cells of the stratum basale meet the papillae of the underlying dermal layer (papillary layer), resulting in the formation of the ridges on your fingers that you recognize as fingerprints. Fingerprints are unique to each individual and are used for forensic analyses because the patterns do not change with the growth and aging processes.

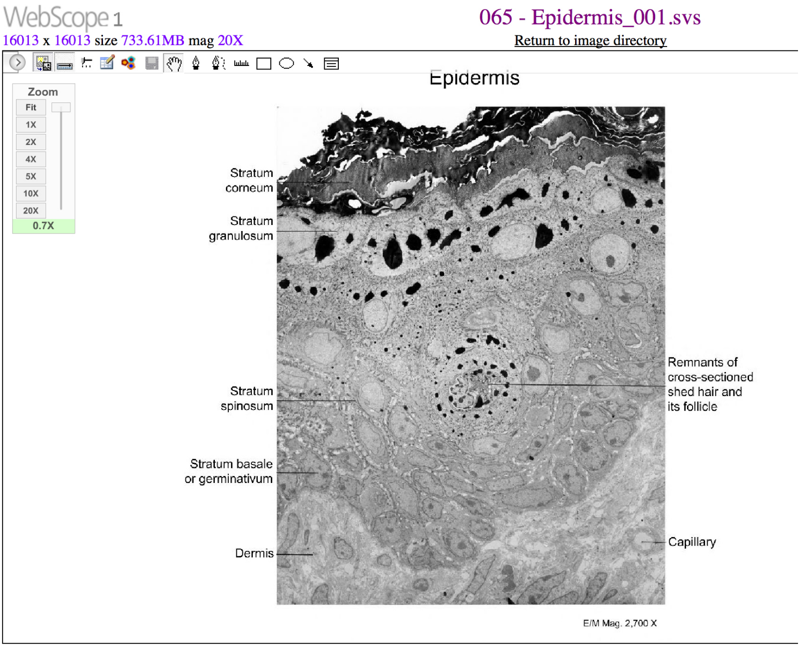
Stratum Spinosum

As the name suggests, the **stratum spinosum** is spiny in appearance due to the protruding cell processes that join the cells via a structure called a **desmosome**. The desmosomes interlock with each other and strengthen the bond between the cells. It is interesting to note that the "spiny" nature of this layer is an artifact of the staining process. Unstained epidermis samples do not exhibit this characteristic appearance. The stratum spinosum is composed of eight to 10 layers of keratinocytes, formed as a result of cell division in the stratum basale ([link]). Interspersed among the keratinocytes of this layer is a type of dendritic cell called the **Langerhans cell**, which functions as a macrophage by engulfing bacteria, foreign particles, and damaged cells that

occur in this layer.

Cells of the Epidermis

The cells in the different layers of the epidermis originate from basal cells located in the stratum basale, yet the cells of each layer are distinctively different. EM × 2700. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail. If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

The keratinocytes in the stratum spinosum begin the synthesis of keratin and release a water-repelling glycolipid that helps prevent water loss from the body, making the skin relatively waterproof. As new keratinocytes are produced atop the stratum basale, the keratinocytes of the stratum spinosum are pushed into the stratum granulosum.

Stratum Granulosum

The **stratum granulosum** has a grainy appearance due to further changes to the keratinocytes as they are pushed from the stratum spinosum. The cells (three to five layers deep) become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin, which is fibrous, and **keratohyalin**, which accumulates as lamellar granules within the cells (see [link]). These two

proteins make up the bulk of the keratinocyte mass in the stratum granulosum and give the layer its grainy appearance. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that will form the stratum lucidum, the stratum corneum, and the accessory structures of hair and nails.

Stratum Lucidum

The **stratum lucidum** is a smooth, seemingly translucent layer of the epidermis located just above the stratum granulosum and below the stratum corneum. This thin layer of cells is found only in the thick skin of the palms, soles, and digits. The keratinocytes that compose the stratum lucidum are dead and flattened (see [link]). These cells are densely packed with **eleiden**, a clear protein rich in lipids, derived from keratohyalin, which gives these cells their transparent (i.e., lucid) appearance and provides a barrier to water.

Stratum Corneum

The **stratum corneum** is the most superficial layer of the epidermis and is the layer exposed to the outside environment (see [link]). The increased keratinization (also called cornification) of the cells in this layer gives it its name. There are usually 15 to 30 layers of cells in the stratum corneum. This

dry, dead layer helps prevent the penetration of microbes and the dehydration of underlying tissues, and provides a mechanical protection against abrasion for the more delicate, underlying layers. Cells in this layer are shed periodically and are replaced by cells pushed up from the stratum granulosum (or stratum lucidum in the case of the palms and soles of feet). The entire layer is replaced during a period of about 4 weeks. Cosmetic procedures, such as microdermabrasion, help remove some of the dry, upper layer and aim to keep the skin looking "fresh" and healthy.

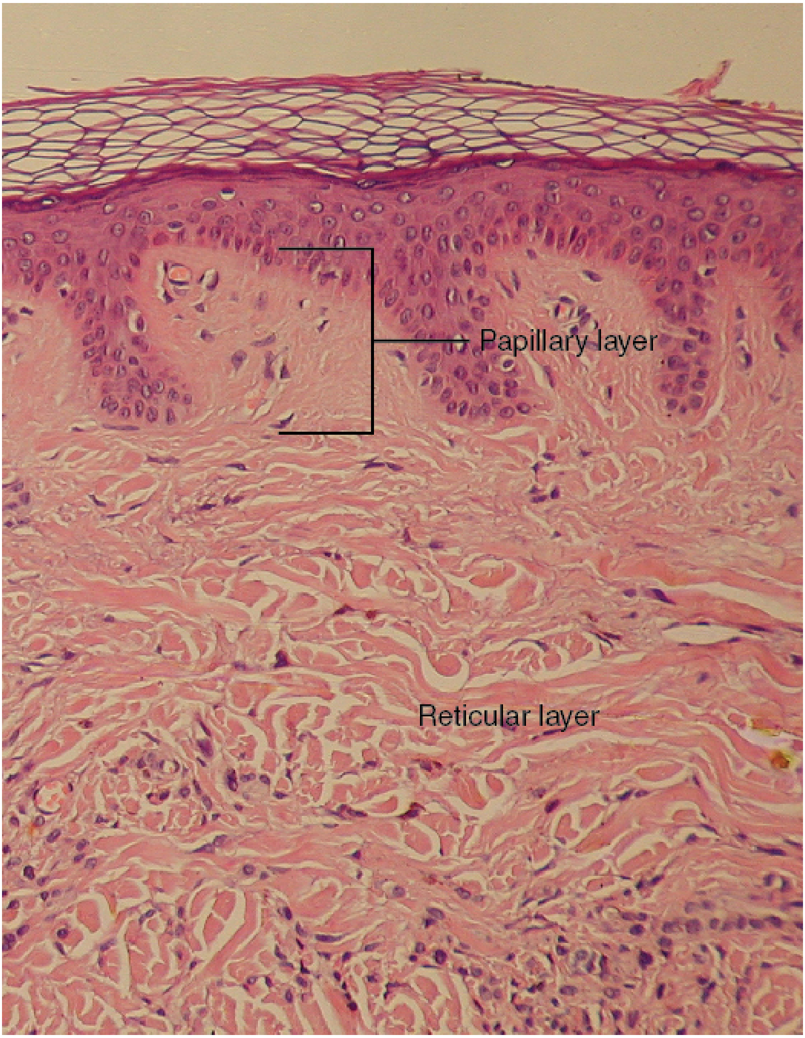
Dermis

The **dermis** might be considered the "core" of the integumentary system (derma- = "skin"), as distinct from the epidermis (epi- = "upon" or "over") and hypodermis (hypo- = "below"). It contains blood and lymph vessels, nerves, and other structures, such as hair follicles and sweat glands. The dermis is made of two layers of connective tissue that compose an interconnected mesh of elastin and collagenous fibers, produced by fibroblasts ([link]).

Layers of the Dermis

This stained slide shows the two components of the dermis—the papillary layer and the reticular layer. Both are made of connective tissue with fibers of collagen extending from one to the other, making the border between the two somewhat indistinct.

The dermal papillae extending into the epidermis belong to the papillary layer, whereas the dense collagen fiber bundles below belong to the reticular layer. LM × 10. (credit: modification of work by "kilbad"/Wikimedia Commons)



Papillary Layer

The **papillary layer** is made of loose, areolar connective tissue, which means the collagen and elastin fibers of this layer form a loose mesh. This superficial layer of the dermis projects into the stratum basale of the epidermis to form finger-like dermal papillae (see [link]). Within the papillary layer are fibroblasts, a small number of fat cells (adipocytes), and an abundance of small blood vessels. In addition, the papillary layer contains phagocytes, defensive cells that help fight bacteria or other infections that have breached the skin. This layer also contains lymphatic capillaries, nerve fibers, and touch receptors called the Meissner corpuscles.

Reticular Layer

Underlying the papillary layer is the much thicker **reticular layer**, composed of dense, irregular connective tissue. This layer is well vascularized and has a rich sensory and sympathetic nerve supply. The reticular layer appears reticulated (net-like) due to a tight meshwork of fibers. **Elastin fibers** provide some elasticity to the skin, enabling movement. Collagen fibers provide structure and tensile strength, with strands of collagen extending into both the papillary layer and the hypodermis. In addition, collagen binds water to keep the skin hydrated. Collagen injections and Retin-A creams help restore skin turgor by either introducing collagen externally or stimulating blood flow and

repair of the dermis, respectively.

Hypodermis

The **hypodermis** (also called the subcutaneous layer or superficial fascia) is a layer directly below the dermis and serves to connect the skin to the underlying fascia (fibrous tissue) of the bones and muscles. It is not strictly a part of the skin, although the border between the hypodermis and dermis can be difficult to distinguish. The hypodermis consists of well-vascularized, loose, areolar connective tissue and adipose tissue, which functions as a mode of fat storage and provides insulation and cushioning for the integument.

Everyday Connection

Lipid Storage

The hypodermis is home to most of the fat that concerns people when they are trying to keep their weight under control. Adipose tissue present in the hypodermis consists of fat-storing cells called adipocytes. This stored fat can serve as an energy reserve, insulate the body to prevent heat loss, and act as a cushion to protect underlying structures from trauma.

Where the fat is deposited and accumulates within the hypodermis depends on hormones

(testosterone, estrogen, insulin, glucagon, leptin, and others), as well as genetic factors. Fat distribution changes as our bodies mature and age. Men tend to accumulate fat in different areas (neck, arms, lower back, and abdomen) than do women (breasts, hips, thighs, and buttocks). The body mass index (BMI) is often used as a measure of fat, although this measure is, in fact, derived from a mathematical formula that compares body weight (mass) to height. Therefore, its accuracy as a health indicator can be called into question in individuals who are extremely physically fit.

In many animals, there is a pattern of storing excess calories as fat to be used in times when food is not readily available. In much of the developed world, insufficient exercise coupled with the ready availability and consumption of high-calorie foods have resulted in unwanted accumulations of adipose tissue in many people. Although periodic accumulation of excess fat may have provided an evolutionary advantage to our ancestors, who experienced unpredictable bouts of famine, it is now becoming chronic and considered a major health threat. Recent studies indicate that a distressing percentage of our population is overweight and/or clinically obese. Not only is this a problem for the individuals affected, but it also has a severe impact on our healthcare system. Changes in lifestyle, specifically in diet and exercise, are the best ways to control body fat accumulation, especially when it reaches levels

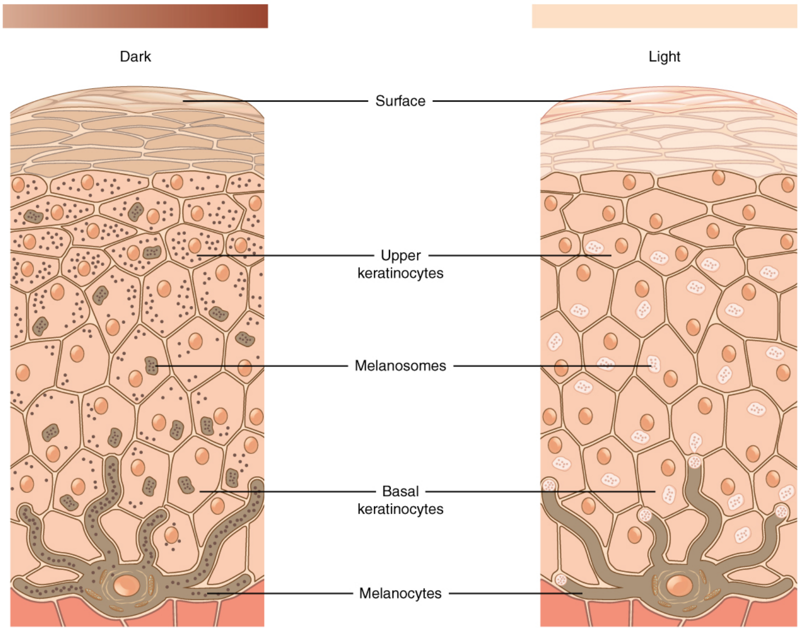
that increase the risk of heart disease and diabetes.

Pigmentation

The color of skin is influenced by a number of pigments, including melanin, carotene, and hemoglobin. Recall that melanin is produced by cells called melanocytes, which are found scattered throughout the stratum basale of the epidermis. The melanin is transferred into the keratinocytes via a cellular vesicle called a **melanosome** ([link]).

Skin Pigmentation

The relative coloration of the skin depends of the amount of melanin produced by melanocytes in the stratum basale and taken up by keratinocytes.



Melanin occurs in two primary forms. Eumelanin exists as black and brown, whereas pheomelanin provides a red color. Dark-skinned individuals produce more melanin than those with pale skin. Exposure to the UV rays of the sun or a tanning salon causes melanin to be manufactured and built up in keratinocytes, as sun exposure stimulates keratinocytes to secrete chemicals that stimulate melanocytes. The accumulation of melanin in keratinocytes results in the darkening of the skin, or a tan. This increased melanin accumulation protects the DNA of epidermal cells from UV ray damage and the breakdown of folic acid, a nutrient necessary for our health and well-being. In contrast, too much melanin can interfere with the production of vitamin D, an important nutrient involved in

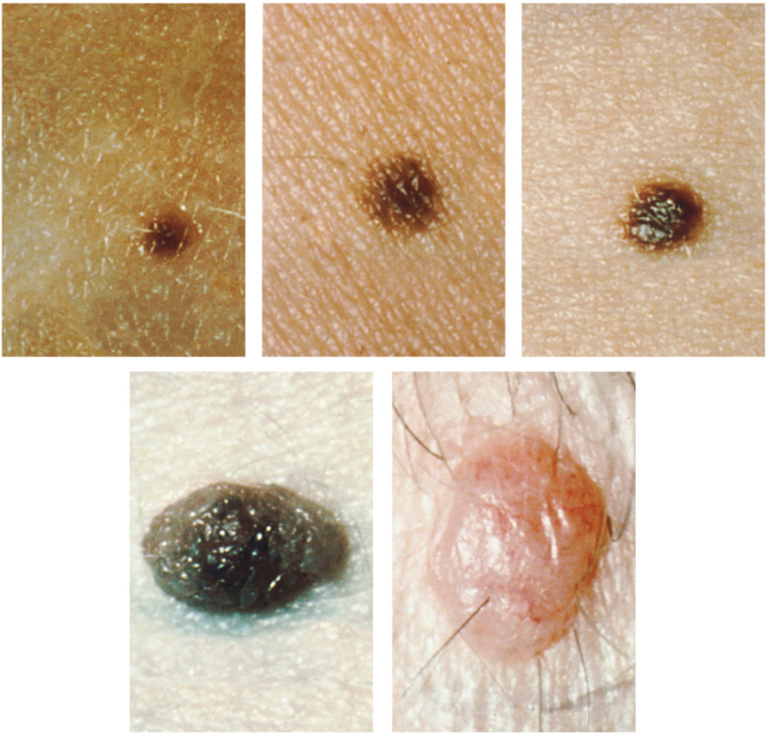
calcium absorption. Thus, the amount of melanin present in our skin is dependent on a balance between available sunlight and folic acid destruction, and protection from UV radiation and vitamin D production.

It requires about 10 days after initial sun exposure for melanin synthesis to peak, which is why pale-skinned individuals tend to suffer sunburns of the epidermis initially. Dark-skinned individuals can also get sunburns, but are more protected than are pale-skinned individuals. Melanosomes are temporary structures that are eventually destroyed by fusion with lysosomes; this fact, along with melanin-filled keratinocytes in the stratum corneum sloughing off, makes tanning impermanent.

Too much sun exposure can eventually lead to wrinkling due to the destruction of the cellular structure of the skin, and in severe cases, can cause sufficient DNA damage to result in skin cancer. When there is an irregular accumulation of melanocytes in the skin, freckles appear. Moles are larger masses of melanocytes, and although most are benign, they should be monitored for changes that might indicate the presence of cancer ([link]).

Moles

Moles range from benign accumulations of melanocytes to melanomas. These structures populate the landscape of our skin. (credit: the National Cancer Institute)



Disorders of the…

Integumentary System

The first thing a clinician sees is the skin, and so the examination of the skin should be part of any thorough physical examination. Most skin disorders are relatively benign, but a few, including melanomas, can be fatal if untreated. A couple of the more noticeable disorders, albinism and vitiligo, affect the appearance of the skin and its accessory organs. Although neither is fatal, it would be hard to claim that they are benign, at

least to the individuals so afflicted.

Albinism is a genetic disorder that affects (completely or partially) the coloring of skin, hair, and eyes. The defect is primarily due to the inability of melanocytes to produce melanin. Individuals with albinism tend to appear white or very pale due to the lack of melanin in their skin and hair. Recall that melanin helps protect the skin from the harmful effects of UV radiation. Individuals with albinism tend to need more protection from UV radiation, as they are more prone to sunburns and skin cancer. They also tend to be more sensitive to light and have vision problems due to the lack of pigmentation on the retinal wall. Treatment of this disorder usually involves addressing the symptoms, such as limiting UV light exposure to the skin and eyes. In **vitiligo**, the melanocytes in certain areas lose their ability to produce melanin, possibly due to an autoimmune reaction. This leads to a loss of color in patches ([link]). Neither albinism nor vitiligo directly affects the lifespan of an individual.

Vitiligo

Individuals with vitiligo experience depigmentation that results in lighter colored patches of skin. The condition is especially noticeable on darker skin. (credit: Klaus D. Peter)

Other changes in the appearance of skin coloration can be indicative of diseases associated with other body systems. Liver disease or liver cancer can cause the accumulation of bile and the yellow pigment bilirubin, leading to the skin appearing yellow or jaundiced (*jaune* is the French word for "yellow"). Tumors of the pituitary gland can result in the secretion of large amounts of melanocyte-stimulating hormone (MSH), which results in a darkening of the skin. Similarly, Addison's disease can stimulate the release of excess amounts of adrenocorticotropic hormone (ACTH), which can give the skin a deep bronze color. A sudden drop in

oxygenation can affect skin color, causing the skin to initially turn ashen (white). With a prolonged reduction in oxygen levels, dark red deoxyhemoglobin becomes dominant in the blood, making the skin appear blue, a condition referred to as cyanosis (*kyanos* is the Greek word for "blue"). This happens when the oxygen supply is restricted, as when someone is experiencing difficulty in breathing because of asthma or a heart attack. However, in these cases the effect on skin color has nothing do with the skin's pigmentation.

This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

Chapter Review

The skin is composed of two major layers: a superficial epidermis and a deeper dermis. The epidermis consists of several layers beginning with the innermost (deepest) stratum basale (germinatum), followed by the stratum spinosum, stratum granulosum, stratum lucidum (when present), and ending with the outermost layer, the stratum corneum. The topmost layer, the stratum corneum, consists of dead cells that shed periodically and is progressively replaced by cells formed from the basal layer. The stratum basale also contains melanocytes, cells that produce melanin, the pigment primarily responsible for giving skin its color. Melanin is transferred to keratinocytes in the stratum spinosum to protect cells from UV rays.

The dermis connects the epidermis to the hypodermis, and provides strength and elasticity due to the presence of collagen and elastin fibers. It has only two layers: the papillary layer with papillae that extend into the epidermis and the lower, reticular layer composed of loose connective tissue. The hypodermis, deep to the dermis of skin, is the connective tissue that connects the dermis to underlying structures; it also harbors adipose tissue for fat storage and protection.

Interactive Link Questions

The skin consists of two layers and a closely associated layer. View this animation to learn more about layers of the skin. What are the basic functions of each of these layers?

The epidermis provides protection, the dermis provides support and flexibility, and the hypodermis (fat layer) provides insulation and padding.

[link] If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

[link] These cells do not have nuclei, so you can deduce that they are dead. They appear to be sloughing off.

[link] If you zoom on the cells of the stratum spinosum, what is distinctive about them?

[link] These cells have desmosomes, which give the cells their spiny appearance.

This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

There are none.

Review Questions

The papillary layer of the dermis is most closely associated with which layer of the epidermis?

1. stratum spinosum
2. stratum corneum
3. stratum granulosum
4. stratum basale

D

Langerhans cells are commonly found in the ______.

1. stratum spinosum

2. stratum corneum
3. stratum granulosum
4. stratum basale

A

The papillary and reticular layers of the dermis are composed mainly of ______.

1. melanocytes
2. keratinocytes
3. connective tissue
4. adipose tissue

C

Collagen lends ______ to the skin.

1. elasticity
2. structure
3. color
4. UV protection

B

Which of the following is not a function of the

hypodermis?

1. protects underlying organs
2. helps maintain body temperature
3. source of blood vessels in the epidermis
4. a site to long-term energy storage

C

Critical Thinking Questions

What determines the color of skin, and what is the process that darkens skin when it is exposed to UV light?

The pigment melanin, produced by melanocytes, is primarily responsible for skin color. Melanin comes in different shades of brown and black. Individuals with darker skin have darker, more abundant melanin, whereas fair-skinned individuals have a lighter shade of skin and less melanin. Exposure to UV irradiation stimulates the melanocytes to produce and secrete more melanin.

Cells of the epidermis derive from stem cells of the stratum basale. Describe how the cells change as they become integrated into the different layers of the epidermis.

As the cells move into the stratum spinosum, they begin the synthesis of keratin and extend cell processes, desmosomes, which link the cells. As the stratum basale continues to produce new cells, the keratinocytes of the stratum spinosum are pushed into the stratum granulosum. The cells become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin and keratohyalin. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that form the stratum lucidum and the stratum corneum. The keratinocytes in these layers are mostly dead and flattened. Cells in the stratum corneum are periodically shed.

Glossary

albinism
: genetic disorder that affects the skin, in which there is no melanin production

basal cell
: type of stem cell found in the stratum basale

and in the hair matrix that continually undergoes cell division, producing the keratinocytes of the epidermis

dermal papilla
: (plural = dermal papillae) extension of the papillary layer of the dermis that increases surface contact between the epidermis and dermis

dermis
: layer of skin between the epidermis and hypodermis, composed mainly of connective tissue and containing blood vessels, hair follicles, sweat glands, and other structures

desmosome
: structure that forms an impermeable junction between cells

elastin fibers
: fibers made of the protein elastin that increase the elasticity of the dermis

eleiden
: clear protein-bound lipid found in the stratum lucidum that is derived from keratohyalin and helps to prevent water loss

epidermis
: outermost tissue layer of the skin

hypodermis
: connective tissue connecting the integument to the underlying bone and muscle

integumentary system
: skin and its accessory structures

keratin
: type of structural protein that gives skin, hair, and nails its hard, water-resistant properties

keratinocyte
: cell that produces keratin and is the most predominant type of cell found in the epidermis

keratohyalin
: granulated protein found in the stratum granulosum

Langerhans cell
: specialized dendritic cell found in the stratum spinosum that functions as a macrophage

melanin
: pigment that determines the color of hair and skin

melanocyte
: cell found in the stratum basale of the epidermis that produces the pigment melanin

melanosome

intercellular vesicle that transfers melanin from melanocytes into keratinocytes of the epidermis

Merkel cell
: receptor cell in the stratum basale of the epidermis that responds to the sense of touch

papillary layer
: superficial layer of the dermis, made of loose, areolar connective tissue

reticular layer
: deeper layer of the dermis; it has a reticulated appearance due to the presence of abundant collagen and elastin fibers

stratum basale
: deepest layer of the epidermis, made of epidermal stem cells

stratum corneum
: most superficial layer of the epidermis

stratum granulosum
: layer of the epidermis superficial to the stratum spinosum

stratum lucidum
: layer of the epidermis between the stratum granulosum and stratum corneum, found only in thick skin covering the palms, soles of the

feet, and digits

stratum spinosum
: layer of the epidermis superficial to the stratum basale, characterized by the presence of desmosomes

vitiligo
: skin condition in which melanocytes in certain areas lose the ability to produce melanin, possibly due an autoimmune reaction that leads to loss of color in patches

Introduction
class="introduction"
Child Looking at Bones

Bone is a living tissue. Unlike the bones of a fossil made inert by a process of mineralization, a child’s bones will continue to grow and develop while contributing to the support and function of other body systems. (credit: James Emery)

Chapter Objectives

After studying this chapter, you will be able to:

- List and describe the functions of bones
- Describe the classes of bones
- Discuss the process of bone formation and

development

- Explain how bone repairs itself after a fracture
- Discuss the effect of exercise, nutrition, and hormones on bone tissue
- Describe how an imbalance of calcium can affect bone tissue

Bones make good fossils. While the soft tissue of a once living organism will decay and fall away over time, bone tissue will, under the right conditions, undergo a process of mineralization, effectively turning the bone to stone. A well-preserved fossil skeleton can give us a good sense of the size and shape of an organism, just as your skeleton helps to define your size and shape. Unlike a fossil skeleton, however, your skeleton is a structure of living tissue that grows, repairs, and renews itself. The bones within it are dynamic and complex organs that serve a number of important functions, including some necessary to maintain homeostasis.

The Functions of the Skeletal System
By the end of this section, you will be able to:

- Define bone, cartilage, and the skeletal system
- List and describe the functions of the skeletal system

Bone, or **osseous tissue**, is a hard, dense connective tissue that forms most of the adult skeleton, the support structure of the body. In the areas of the skeleton where bones move (for example, the ribcage and joints), **cartilage**, a semi-rigid form of connective tissue, provides flexibility and smooth surfaces for movement. The **skeletal system** is the body system composed of bones and cartilage and performs the following critical functions for the human body:

- supports the body
- facilitates movement
- protects internal organs
- produces blood cells
- stores and releases minerals and fat

Support, Movement, and Protection

The most apparent functions of the skeletal system are the gross functions—those visible by

observation. Simply by looking at a person, you can see how the bones support, facilitate movement, and protect the human body.

Just as the steel beams of a building provide a scaffold to support its weight, the bones and cartilage of your skeletal system compose the scaffold that supports the rest of your body. Without the skeletal system, you would be a limp mass of organs, muscle, and skin.

Bones also facilitate movement by serving as points of attachment for your muscles. While some bones only serve as a support for the muscles, others also transmit the forces produced when your muscles contract. From a mechanical point of view, bones act as levers and joints serve as fulcrums ([link]). Unless a muscle spans a joint and contracts, a bone is not going to move. For information on the interaction of the skeletal and muscular systems, that is, the musculoskeletal system, seek additional content.

Bones Support Movement

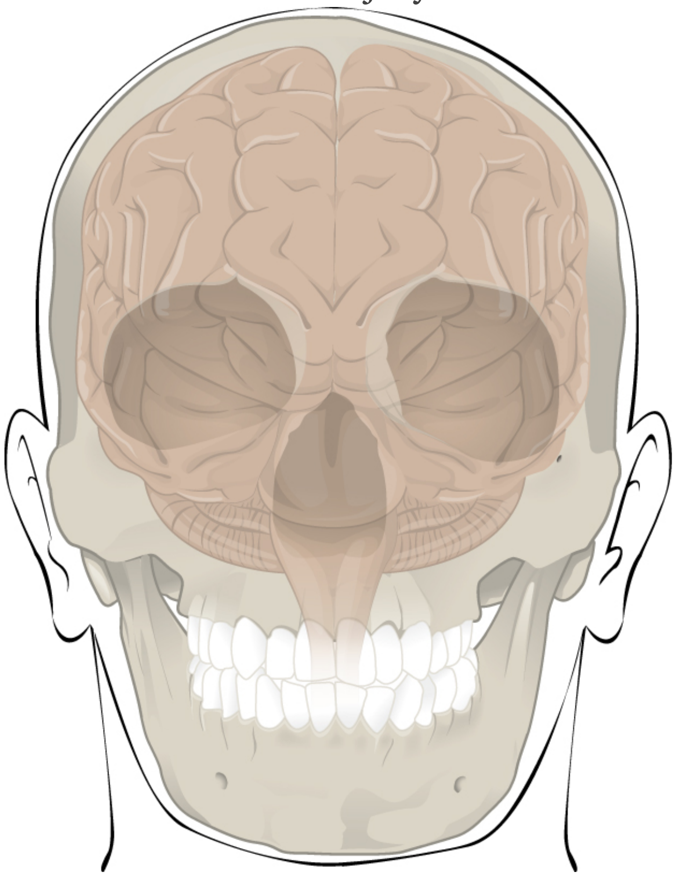
Bones act as levers when muscles span a joint and contract. (credit: Benjamin J. DeLong)

Bones also protect internal organs from injury by covering or surrounding them. For example, your ribs protect your lungs and heart, the bones of your vertebral column (spine) protect your spinal cord, and the bones of your cranium (skull) protect your

brain ([link]).

Bones Protect Brain

The cranium completely surrounds and protects the brain from non-traumatic injury.



Career Connection

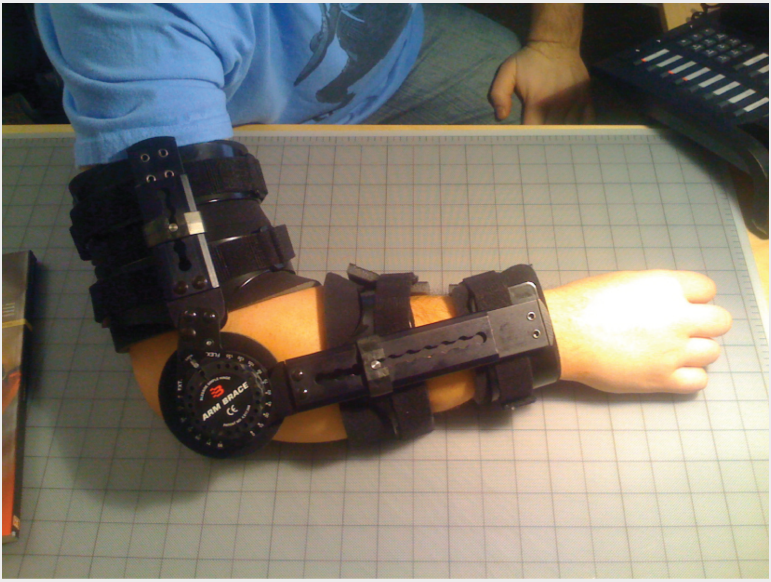
Orthopedist

An **orthopedist** is a doctor who specializes in diagnosing and treating disorders and injuries related to the musculoskeletal system. Some

orthopedic problems can be treated with medications, exercises, braces, and other devices, but others may be best treated with surgery ([link]).

Arm Brace

An orthopedist will sometimes prescribe the use of a brace that reinforces the underlying bone structure it is being used to support. (credit: Juhan Sonin)



While the origin of the word “orthopedics” (ortho- = “straight”; paed- = “child”), literally means “straightening of the child,” orthopedists can have patients who range from pediatric to geriatric. In recent years, orthopedists have even performed prenatal surgery to correct spina bifida, a congenital defect in which the neural canal in the spine of the fetus fails to close completely during embryologic development.

Orthopedists commonly treat bone and joint injuries but they also treat other bone conditions including curvature of the spine. Lateral curvatures (scoliosis) can be severe enough to slip under the shoulder blade (scapula) forcing it up as a hump. Spinal curvatures can also be excessive dorsoventrally (kyphosis) causing a hunch back and thoracic compression. These curvatures often appear in preteens as the result of poor posture, abnormal growth, or indeterminate causes. Mostly, they are readily treated by orthopedists. As people age, accumulated spinal column injuries and diseases like osteoporosis can also lead to curvatures of the spine, hence the stooping you sometimes see in the elderly.

Some orthopedists sub-specialize in sports medicine, which addresses both simple injuries, such as a sprained ankle, and complex injuries, such as a torn rotator cuff in the shoulder. Treatment can range from exercise to surgery.

Mineral Storage, Energy Storage, and Hematopoiesis

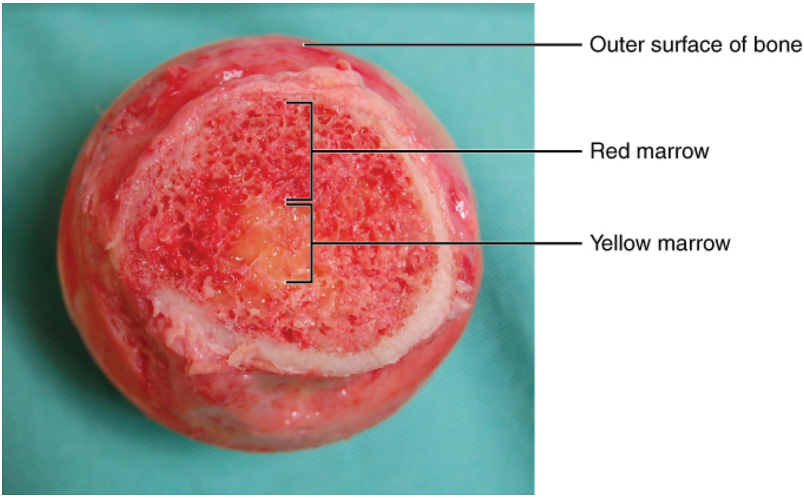
On a metabolic level, bone tissue performs several critical functions. For one, the bone matrix acts as a reservoir for a number of minerals important to the

functioning of the body, especially calcium, and phosphorus. These minerals, incorporated into bone tissue, can be released back into the bloodstream to maintain levels needed to support physiological processes. Calcium ions, for example, are essential for muscle contractions and controlling the flow of other ions involved in the transmission of nerve impulses.

Bone also serves as a site for fat storage and blood cell production. The softer connective tissue that fills the interior of most bone is referred to as bone marrow ([link]). There are two types of bone marrow: yellow marrow and red marrow. **Yellow marrow** contains adipose tissue; the triglycerides stored in the adipocytes of the tissue can serve as a source of energy. **Red marrow** is where **hematopoiesis**—the production of blood cells—takes place. Red blood cells, white blood cells, and platelets are all produced in the red marrow.

Head of Femur Showing Red and Yellow Marrow

The head of the femur contains both yellow and red marrow. Yellow marrow stores fat. Red marrow is responsible for hematopoiesis. (credit: modification of work by "stevenfruitsmaak"/Wikimedia Commons)



Chapter Review

The major functions of the bones are body support, facilitation of movement, protection of internal organs, storage of minerals and fat, and hematopoiesis. Together, the muscular system and skeletal system are known as the musculoskeletal system.

Review Questions

Which function of the skeletal system would be especially important if you were in a car accident?

1. storage of minerals
2. protection of internal organs
3. facilitation of movement
4. fat storage

B

Bone tissue can be described as ______.

1. dead calcified tissue
2. cartilage
3. the skeletal system
4. dense, hard connective tissue

D

Without red marrow, bones would not be able to ______.

1. store phosphate
2. store calcium
3. make blood cells
4. move like levers

C

Yellow marrow has been identified as _____.

1. an area of fat storage
2. a point of attachment for muscles
3. the hard portion of bone
4. the cause of kyphosis

A

Which of the following can be found in areas of movement?

1. hematopoiesis
2. cartilage
3. yellow marrow
4. red marrow

B

The skeletal system is made of _____.

1. muscles and tendons
2. bones and cartilage
3. vitreous humor
4. minerals and fat

B

Critical Thinking Questions

The skeletal system is composed of bone and cartilage and has many functions. Choose three of these functions and discuss what features of the skeletal system allow it to accomplish these functions.

It supports the body. The rigid, yet flexible skeleton acts as a framework to support the other organs of the body.

It facilitates movement. The movable joints allow the skeleton to change shape and positions; that is, move.

It protects internal organs. Parts of the skeleton enclose or partly enclose various organs of the body including our brain, ears, heart, and lungs. Any trauma to these organs has to be mediated through the skeletal system.

It produces blood cells. The central cavity of long bones is filled with marrow. The red marrow is responsible for forming red and white blood cells.

It stores and releases minerals and fat. The mineral component of bone, in addition to providing hardness to bone, provides a mineral reservoir that can be tapped as needed. Additionally, the yellow marrow, which is found in the central cavity of long bones along with red marrow, serves as a storage site for fat.

Glossary

bone
: hard, dense connective tissue that forms the structural elements of the skeleton

cartilage
: semi-rigid connective tissue found on the skeleton in areas where flexibility and smooth surfaces support movement

hematopoiesis
: production of blood cells, which occurs in the red marrow of the bones

orthopedist
: doctor who specializes in diagnosing and treating musculoskeletal disorders and injuries

osseous tissue
: bone tissue; a hard, dense connective tissue that forms the structural elements of the

skeleton

red marrow
: connective tissue in the interior cavity of a bone where hematopoiesis takes place

skeletal system
: organ system composed of bones and cartilage that provides for movement, support, and protection

yellow marrow
: connective tissue in the interior cavity of a bone where fat is stored

Bone Classification

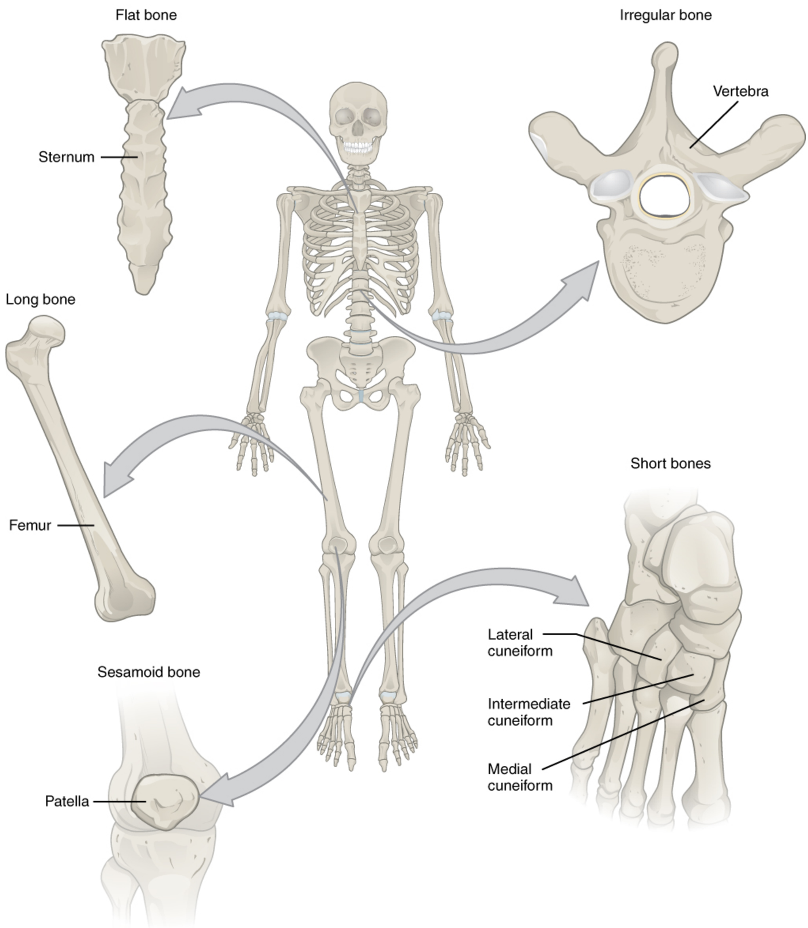
By the end of this section, you will be able to:

- Classify bones according to their shapes
- Describe the function of each category of bones

The 206 bones that compose the adult skeleton are divided into five categories based on their shapes ([link]). Their shapes and their functions are related such that each categorical shape of bone has a distinct function.

Classifications of Bones

Bones are classified according to their shape.



Long Bones

A **long bone** is one that is cylindrical in shape, being longer than it is wide. Keep in mind, however, that the term describes the shape of a bone, not its size. Long bones are found in the arms (humerus, ulna, radius) and legs (femur, tibia, fibula), as well as in the fingers (metacarpals, phalanges) and toes

(metatarsals, phalanges). Long bones function as levers; they move when muscles contract.

Short Bones

A **short bone** is one that is cube-like in shape, being approximately equal in length, width, and thickness. The only short bones in the human skeleton are in the carpals of the wrists and the tarsals of the ankles. Short bones provide stability and support as well as some limited motion.

Flat Bones

The term "**flat bone**" is somewhat of a misnomer because, although a flat bone is typically thin, it is also often curved. Examples include the cranial (skull) bones, the scapulae (shoulder blades), the sternum (breastbone), and the ribs. Flat bones serve as points of attachment for muscles and often protect internal organs.

Irregular Bones

An **irregular bone** is one that does not have any easily characterized shape and therefore does not fit any other classification. These bones tend to have

more complex shapes, like the vertebrae that support the spinal cord and protect it from compressive forces. Many facial bones, particularly the ones containing sinuses, are classified as irregular bones.

Sesamoid Bones

A **sesamoid bone** is a small, round bone that, as the name suggests, is shaped like a sesame seed. These bones form in tendons (the sheaths of tissue that connect bones to muscles) where a great deal of pressure is generated in a joint. The sesamoid bones protect tendons by helping them overcome compressive forces. Sesamoid bones vary in number and placement from person to person but are typically found in tendons associated with the feet, hands, and knees. The patellae (singular = patella) are the only sesamoid bones found in common with every person. [link] reviews bone classifications with their associated features, functions, and examples.

Bone Classifications

Bone classification	Features	Function(s)	Examples
Long	Cylinder-like shape, longer than it is wide	Leverage	Femur, tibia, fibula, metatarsals, humerus, ulna, radius, metacarpals, phalanges
Short	Cube-like shape, approximately equal in length, width, and thickness	Provide stability, support, while allowing for some motion	Carpals, tarsals
Flat	Thin and curved	Points of attachment for muscles; protectors of internal organs	Sternum, ribs, scapulae, cranial bones
Irregular	Complex shape	Protect internal organs	Vertebrae, facial bones
Sesamoid	Small and round; embedded in tendons	Protect tendons from compressive forces	Patellae

Chapter Review

Bones can be classified according to their shapes. Long bones, such as the femur, are longer than they are wide. Short bones, such as the carpals, are approximately equal in length, width, and thickness. Flat bones are thin, but are often curved, such as the ribs. Irregular bones such as those of the face have no characteristic shape. Sesamoid bones, such as the patellae, are small and round, and are located in tendons.

Review Questions

Most of the bones of the arms and hands are long bones; however, the bones in the wrist are categorized as ______.

1. flat bones
2. short bones
3. sesamoid bones
4. irregular bones

B

Sesamoid bones are found embedded in ______.

1. joints
2. muscles
3. ligaments
4. tendons

D

Bones that surround the spinal cord are classified as ______ bones.

1. irregular
2. sesamoid
3. flat
4. short

A

Which category of bone is among the most numerous in the skeleton?

1. long bone
2. sesamoid bone
3. short bone
4. flat bone

A

Long bones enable body movement by acting as a ______.

1. counterweight
2. resistive force
3. lever
4. fulcrum

C

Critical Thinking Questions

What are the structural and functional differences between a tarsal and a metatarsal?

Structurally, a tarsal is a short bone, meaning its length, width, and thickness are about equal, while a metatarsal is a long bone whose length is greater than its width. Functionally, the tarsal provides limited motion, while the metatarsal acts as a lever.

What are the structural and functional

differences between the femur and the patella?

Structurally, the femur is a long bone, meaning its length is greater than its width, while the patella, a sesamoid bone, is small and round. Functionally, the femur acts as a lever, while the patella protects the patellar tendon from compressive forces.

Glossary

flat bone
: thin and curved bone; serves as a point of attachment for muscles and protects internal organs

irregular bone
: bone of complex shape; protects internal organs from compressive forces

long bone
: cylinder-shaped bone that is longer than it is wide; functions as a lever

sesamoid bone
: small, round bone embedded in a tendon; protects the tendon from compressive forces

short bone
: cube-shaped bone that is approximately equal

in length, width, and thickness; provides limited motion

Bone Structure
By the end of this section, you will be able to:

- Identify the anatomical features of a bone
- Define and list examples of bone markings
- Describe the histology of bone tissue
- Compare and contrast compact and spongy bone
- Identify the structures that compose compact and spongy bone
- Describe how bones are nourished and innervated

Bone tissue (osseous tissue) differs greatly from other tissues in the body. Bone is hard and many of its functions depend on that characteristic hardness. Later discussions in this chapter will show that bone is also dynamic in that its shape adjusts to accommodate stresses. This section will examine the gross anatomy of bone first and then move on to its histology.

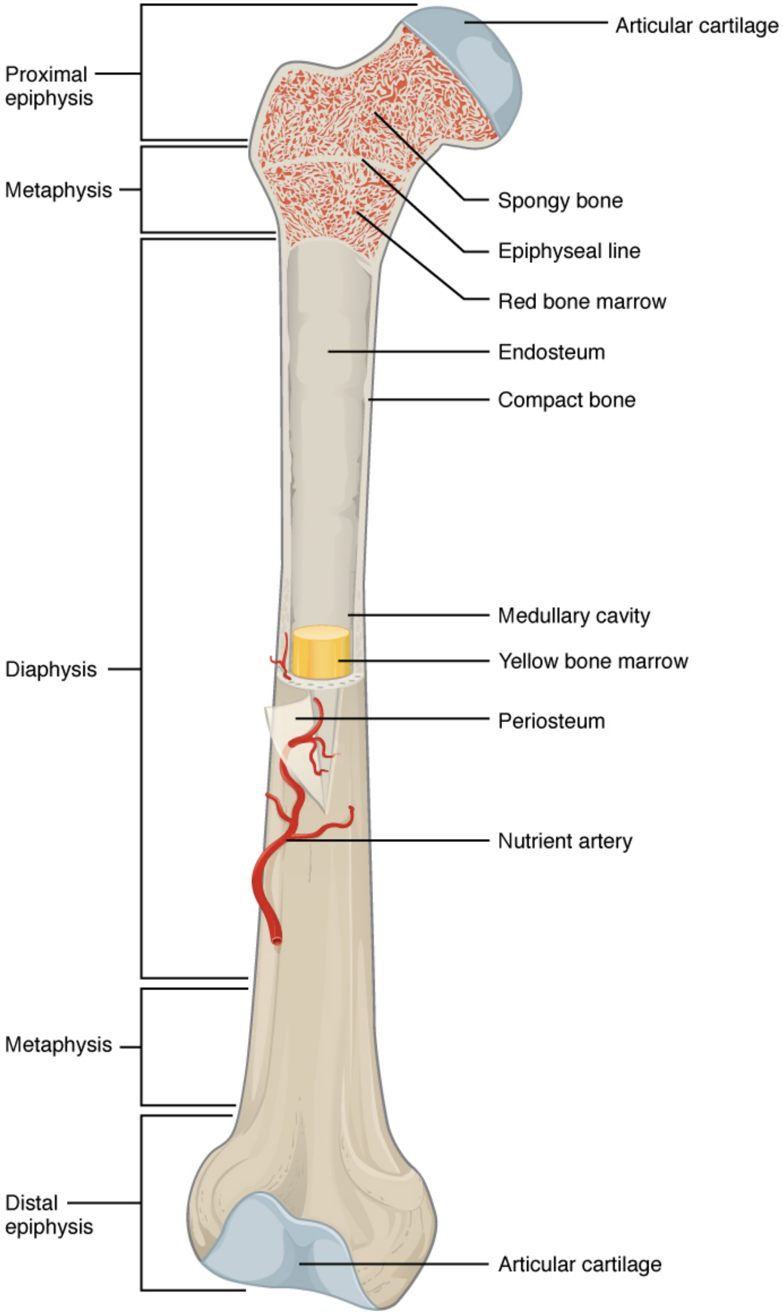
Gross Anatomy of Bone

The structure of a long bone allows for the best visualization of all of the parts of a bone ([link]). A long bone has two parts: the **diaphysis** and the **epiphysis**. The diaphysis is the tubular shaft that runs between the proximal and distal ends of the

bone. The hollow region in the diaphysis is called the **medullary cavity**, which is filled with yellow marrow. The walls of the diaphysis are composed of dense and hard **compact bone**.

Anatomy of a Long Bone

A typical long bone shows the gross anatomical characteristics of bone.



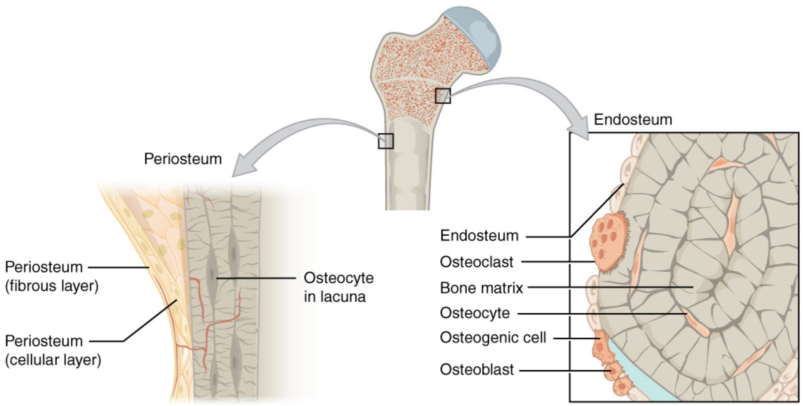
The wider section at each end of the bone is called

the epiphysis (plural = epiphyses), which is filled with spongy bone. Red marrow fills the spaces in the spongy bone. Each epiphysis meets the diaphysis at the metaphysis, the narrow area that contains the **epiphyseal plate** (growth plate), a layer of hyaline (transparent) cartilage in a growing bone. When the bone stops growing in early adulthood (approximately 18–21 years), the cartilage is replaced by osseous tissue and the epiphyseal plate becomes an epiphyseal line.

The medullary cavity has a delicate membranous lining called the **endosteum** (end- = “inside”; oste- = “bone”), where bone growth, repair, and remodeling occur. The outer surface of the bone is covered with a fibrous membrane called the **periosteum** (peri- = “around” or “surrounding”). The periosteum contains blood vessels, nerves, and lymphatic vessels that nourish compact bone. Tendons and ligaments also attach to bones at the periosteum. The periosteum covers the entire outer surface except where the epiphyses meet other bones to form joints ([link]). In this region, the epiphyses are covered with **articular cartilage**, a thin layer of cartilage that reduces friction and acts as a shock absorber.

Periosteum and Endosteum

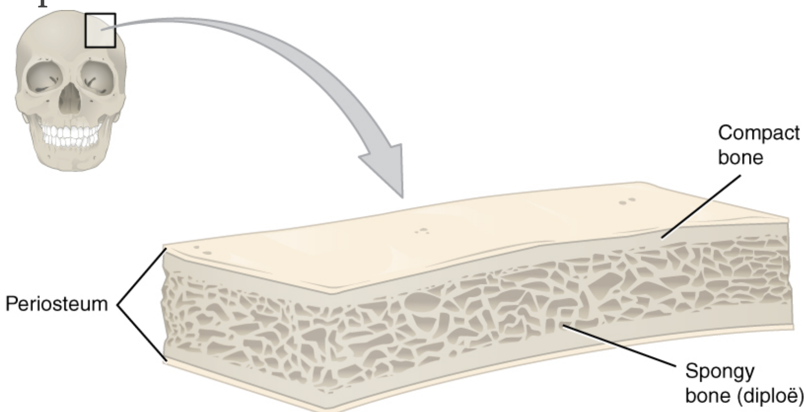
The periosteum forms the outer surface of bone, and the endosteum lines the medullary cavity.



Flat bones, like those of the cranium, consist of a layer of **diploë** (spongy bone), lined on either side by a layer of compact bone ([link]). The two layers of compact bone and the interior spongy bone work together to protect the internal organs. If the outer layer of a cranial bone fractures, the brain is still protected by the intact inner layer.

Anatomy of a Flat Bone

This cross-section of a flat bone shows the spongy bone (diploë) lined on either side by a layer of compact bone.



Bone Markings

The surface features of bones vary considerably, depending on the function and location in the body. [link] describes the bone markings, which are illustrated in ([link]). There are three general classes of bone markings: (1) articulations, (2) projections, and (3) holes. As the name implies, an **articulation** is where two bone surfaces come together (articulus = “joint”). These surfaces tend to conform to one another, such as one being rounded and the other cupped, to facilitate the function of the articulation. A **projection** is an area of a bone that projects above the surface of the bone. These are the attachment points for tendons and ligaments. In general, their size and shape is an indication of the forces exerted through the attachment to the bone. A **hole** is an opening or groove in the bone that allows blood vessels and nerves to enter the bone. As with the other markings, their size and shape reflect the size of the vessels and nerves that penetrate the bone at these points.

Bone Markings

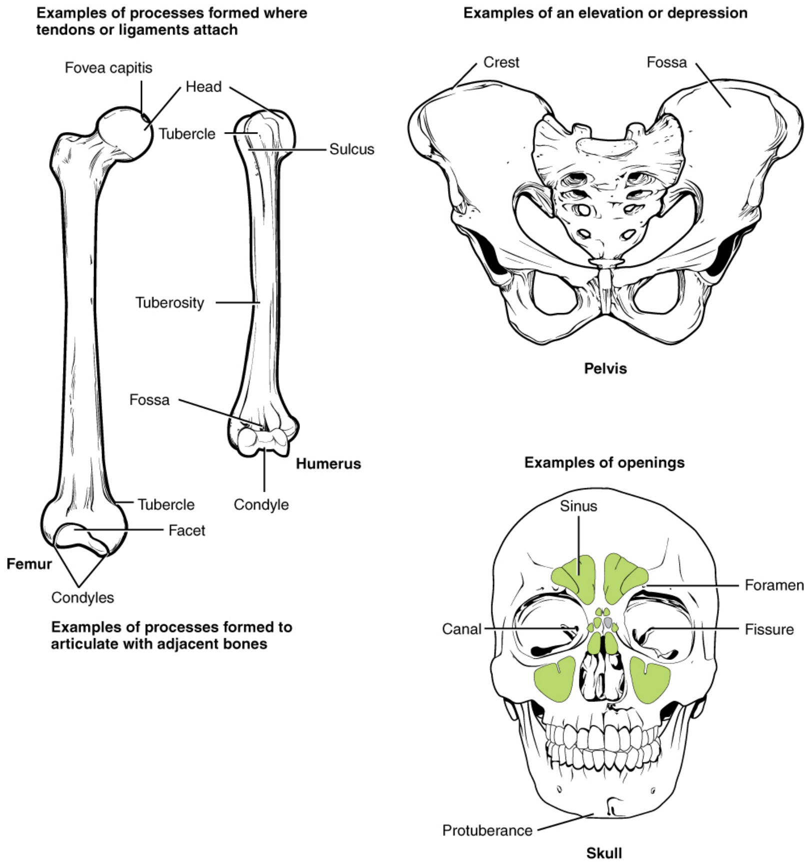
Marking	Description	Example

Articulations	Where two bones meet	Knee joint
Head	Prominent rounded surface	Head of femur
Facet	Flat surface	Vertebrae
Condyle	Rounded surface	Occipital condyles
Projections	Raised markings	Spinous process of the vertebrae
Protuberance	Protruding	Chin
Process	Prominence feature	Transverse process of vertebra
Spine	Sharp process	Ischial spine
Tubercle	Small, rounded process	Tubercle of humerus
Tuberosity	Rough surface	Deltoid tuberosity
Line	Slight, elongated ridge	Temporal lines of the parietal bones
Crest	Ridge	Iliac crest
Holes	Holes and depressions	Foramen (holes through which blood vessels can pass through)
Fossa	Elongated basin	Mandibular fossa
Fovea	Small pit	Fovea capitis on the head of the femur
Sulcus	Groove	Sigmoid sulcus of

		the temporal bones
Canal	Passage in bone	Auditory canal
Fissure	Slit through bone	Auricular fissure
Foramen	Hole through bone	Foramen magnum in the occipital bone
Meatus	Opening into canal	External auditory meatus
Sinus	Air-filled space in bone	Nasal sinus

Bone Features

The surface features of bones depend on their function, location, attachment of ligaments and tendons, or the penetration of blood vessels and nerves.



Bone Cells and Tissue

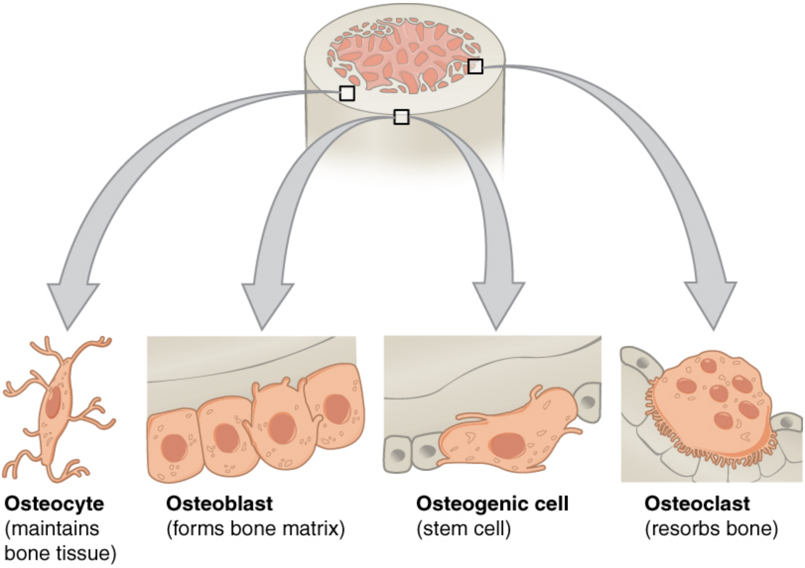
Bone contains a relatively small number of cells entrenched in a matrix of collagen fibers that provide a surface for inorganic salt crystals to adhere. These salt crystals form when calcium phosphate and calcium carbonate combine to create hydroxyapatite, which incorporates other inorganic salts like magnesium hydroxide, fluoride, and sulfate as it crystallizes, or calcifies, on the collagen

fibers. The hydroxyapatite crystals give bones their hardness and strength, while the collagen fibers give them flexibility so that they are not brittle.

Although bone cells compose a small amount of the bone volume, they are crucial to the function of bones. Four types of cells are found within bone tissue: osteoblasts, osteocytes, osteogenic cells, and osteoclasts ([link]).

Bone Cells

Four types of cells are found within bone tissue. Osteogenic cells are undifferentiated and develop into osteoblasts. When osteoblasts get trapped within the calcified matrix, their structure and function changes, and they become osteocytes. Osteoclasts develop from monocytes and macrophages and differ in appearance from other bone cells.



The **osteoblast** is the bone cell responsible for forming new bone and is found in the growing portions of bone, including the periosteum and endosteum. Osteoblasts, which do not divide, synthesize and secrete the collagen matrix and calcium salts. As the secreted matrix surrounding the osteoblast calcifies, the osteoblast become trapped within it; as a result, it changes in structure and becomes an **osteocyte**, the primary cell of mature bone and the most common type of bone cell. Each osteocyte is located in a space called a **lacuna** and is surrounded by bone tissue. Osteocytes maintain the mineral concentration of the matrix via the secretion of enzymes. Like osteoblasts, osteocytes lack mitotic activity. They can communicate with each other and receive nutrients via long cytoplasmic processes that extend through **canaliculi** (singular = canaliculus), channels within the bone matrix.

If osteoblasts and osteocytes are incapable of mitosis, then how are they replenished when old ones die? The answer lies in the properties of a third category of bone cells—the **osteogenic cell**. These osteogenic cells are undifferentiated with high mitotic activity and they are the only bone cells that divide. Immature osteogenic cells are found in the deep layers of the periosteum and the marrow. They differentiate and develop into osteoblasts.

The dynamic nature of bone means that new tissue

is constantly formed, and old, injured, or unnecessary bone is dissolved for repair or for calcium release. The cell responsible for bone resorption, or breakdown, is the **osteoclast**. They are found on bone surfaces, are multinucleated, and originate from monocytes and macrophages, two types of white blood cells, not from osteogenic cells. Osteoclasts are continually breaking down old bone while osteoblasts are continually forming new bone. The ongoing balance between osteoblasts and osteoclasts is responsible for the constant but subtle reshaping of bone. [link] reviews the bone cells, their functions, and locations.

Bone Cells

Cell type	Function	Location
Osteogenic cells	Develop into osteoblasts	Deep layers of the periosteum and the marrow
Osteoblasts	Bone formation	Growing portions of bone, including periosteum and endosteum
Osteocytes	Maintain mineral concentration of matrix	Entrapped in matrix

Osteoclasts	Bone resorption	Bone surfaces and at sites of old, injured, or unneeded bone

Compact and Spongy Bone

The differences between compact and spongy bone are best explored via their histology. Most bones contain compact and spongy osseous tissue, but their distribution and concentration vary based on the bone's overall function. Compact bone is dense so that it can withstand compressive forces, while spongy (cancellous) bone has open spaces and supports shifts in weight distribution.

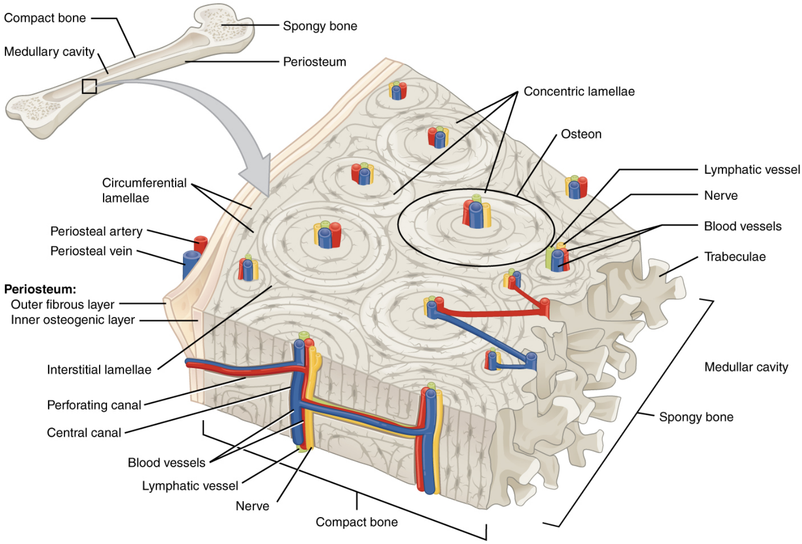
Compact Bone

Compact bone is the denser, stronger of the two types of bone tissue ([link]). It can be found under the periosteum and in the diaphyses of long bones, where it provides support and protection.

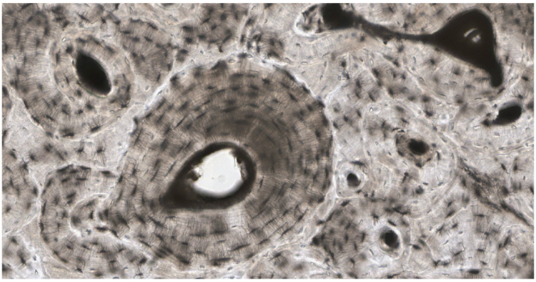
Diagram of Compact Bone

(a) This cross-sectional view of compact bone shows the basic structural unit, the osteon. (b) In this micrograph of the osteon, you can clearly see the concentric lamellae and central canals. LM × 40. (Micrograph provided by the Regents of University

of Michigan Medical School © 2012)



(a)



(b)

The microscopic structural unit of compact bone is called an **osteon**, or Haversian system. Each osteon is composed of concentric rings of calcified matrix called lamellae (singular = lamella). Running down the center of each osteon is the **central canal**, or Haversian canal, which contains blood vessels, nerves, and lymphatic vessels. These vessels and nerves branch off at right angles through a

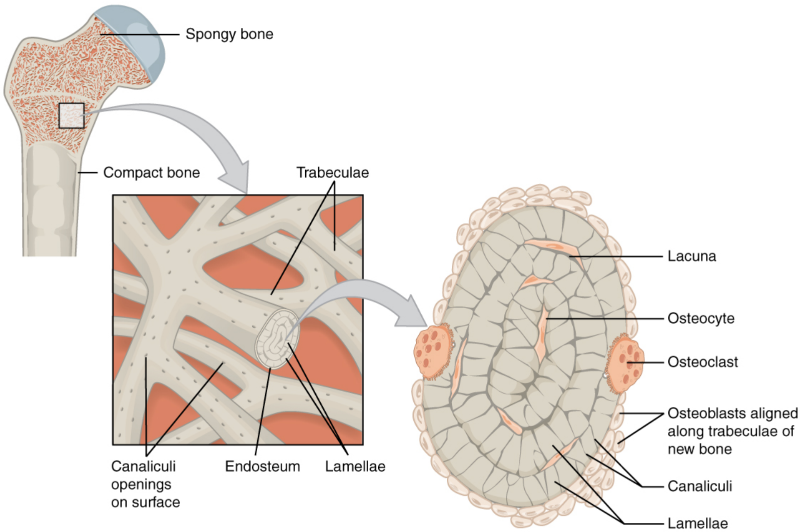
perforating canal, also known as Volkmann's canals, to extend to the periosteum and endosteum.

The osteocytes are located inside spaces called lacunae (singular = lacuna), found at the borders of adjacent lamellae. As described earlier, canaliculi connect with the canaliculi of other lacunae and eventually with the central canal. This system allows nutrients to be transported to the osteocytes and wastes to be removed from them.

Spongy (Cancellous) Bone

Like compact bone, **spongy bone**, also known as cancellous bone, contains osteocytes housed in lacunae, but they are not arranged in concentric circles. Instead, the lacunae and osteocytes are found in a lattice-like network of matrix spikes called **trabeculae** (singular = trabecula) ([link]). The trabeculae may appear to be a random network, but each trabecula forms along lines of stress to provide strength to the bone. The spaces of the trabeculated network provide balance to the dense and heavy compact bone by making bones lighter so that muscles can move them more easily. In addition, the spaces in some spongy bones contain red marrow, protected by the trabeculae, where hematopoiesis occurs.
Diagram of Spongy Bone
Spongy bone is composed of trabeculae that contain the osteocytes. Red marrow fills the spaces in some

bones.



Aging and the...

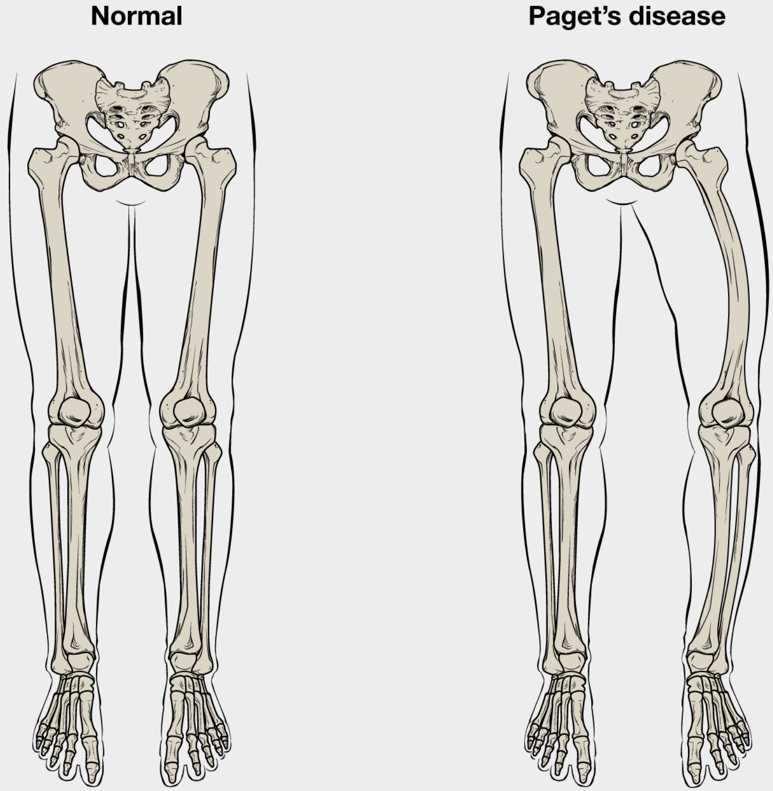
Skeletal System: Paget’s Disease

Paget’s disease usually occurs in adults over age 40. It is a disorder of the bone remodeling process that begins with overactive osteoclasts. This means more bone is resorbed than is laid down. The osteoblasts try to compensate but the new bone they lay down is weak and brittle and therefore prone to fracture.

While some people with Paget’s disease have no symptoms, others experience pain, bone fractures, and bone deformities ([link]). Bones of the pelvis, skull, spine, and legs are the most commonly affected. When occurring in the skull, Paget’s disease can cause headaches and hearing loss.

Paget's Disease

Normal leg bones are relatively straight, but those affected by Paget’s disease are porous and curved.



What causes the osteoclasts to become overactive? The answer is still unknown, but hereditary factors seem to play a role. Some scientists believe Paget’s disease is due to an as-yet-unidentified virus. Paget’s disease is diagnosed via imaging studies and lab tests. X-rays may show bone deformities or areas of bone resorption. Bone scans are also useful. In these studies, a dye containing a radioactive ion is injected into the body. Areas of bone resorption have an affinity for the ion, so they will light up on the scan if the ions are absorbed. In

addition, blood levels of an enzyme called alkaline phosphatase are typically elevated in people with Paget’s disease.

Bisphosphonates, drugs that decrease the activity of osteoclasts, are often used in the treatment of Paget’s disease. However, in a small percentage of cases, bisphosphonates themselves have been linked to an increased risk of fractures because the old bone that is left after bisphosphonates are administered becomes worn out and brittle. Still, most doctors feel that the benefits of bisphosphonates more than outweigh the risk; the medical professional has to weigh the benefits and risks on a case-by-case basis. Bisphosphonate treatment can reduce the overall risk of deformities or fractures, which in turn reduces the risk of surgical repair and its associated risks and complications.

Blood and Nerve Supply

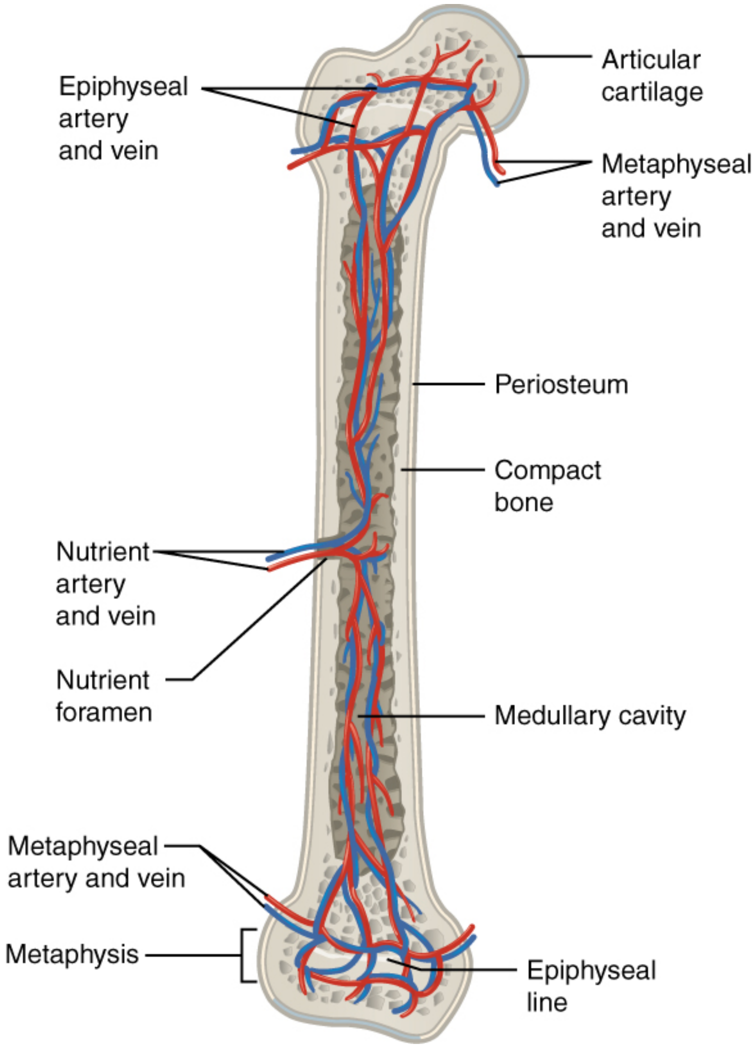
The spongy bone and medullary cavity receive nourishment from arteries that pass through the compact bone. The arteries enter through the **nutrient foramen** (plural = foramina), small openings in the diaphysis ([link]). The osteocytes in spongy bone are nourished by blood vessels of the

periosteum that penetrate spongy bone and blood that circulates in the marrow cavities. As the blood passes through the marrow cavities, it is collected by veins, which then pass out of the bone through the foramina.

In addition to the blood vessels, nerves follow the same paths into the bone where they tend to concentrate in the more metabolically active regions of the bone. The nerves sense pain, and it appears the nerves also play roles in regulating blood supplies and in bone growth, hence their concentrations in metabolically active sites of the bone.

Diagram of Blood and Nerve Supply to Bone

Blood vessels and nerves enter the bone through the nutrient foramen.


Epiphyseal artery and vein
Articular cartilage
Metaphyseal artery and vein
Periosteum
Compact bone
Nutrient artery and vein
Nutrient foramen
Medullary cavity
Metaphyseal artery and vein
Metaphysis
Epiphyseal line

Watch this video to see the microscopic features of a bone.

Chapter Review

A hollow medullary cavity filled with yellow marrow runs the length of the diaphysis of a long bone. The walls of the diaphysis are compact bone. The epiphyses, which are wider sections at each end of a long bone, are filled with spongy bone and red marrow. The epiphyseal plate, a layer of hyaline cartilage, is replaced by osseous tissue as the organ grows in length. The medullary cavity has a delicate membranous lining called the endosteum. The outer surface of bone, except in regions covered with articular cartilage, is covered with a fibrous membrane called the periosteum. Flat bones consist of two layers of compact bone surrounding a layer of spongy bone. Bone markings depend on the function and location of bones. Articulations are places where two bones meet. Projections stick out

from the surface of the bone and provide attachment points for tendons and ligaments. Holes are openings or depressions in the bones.

Bone matrix consists of collagen fibers and organic ground substance, primarily hydroxyapatite formed from calcium salts. Osteogenic cells develop into osteoblasts. Osteoblasts are cells that make new bone. They become osteocytes, the cells of mature bone, when they get trapped in the matrix. Osteoclasts engage in bone resorption. Compact bone is dense and composed of osteons, while spongy bone is less dense and made up of trabeculae. Blood vessels and nerves enter the bone through the nutrient foramina to nourish and innervate bones.

Review Questions

Which of the following occurs in the spongy bone of the epiphysis?

1. bone growth
2. bone remodeling
3. hematopoiesis
4. shock absorption

C

The diaphysis contains ______.

1. the metaphysis
2. fat stores
3. spongy bone
4. compact bone

B

The fibrous membrane covering the outer surface of the bone is the ______.

1. periosteum
2. epiphysis
3. endosteum
4. diaphysis

A

Which of the following are incapable of undergoing mitosis?

1. osteoblasts and osteoclasts
2. osteocytes and osteoclasts
3. osteoblasts and osteocytes
4. osteogenic cells and osteoclasts

C

Which cells do not originate from osteogenic cells?

1. osteoblasts
2. osteoclasts
3. osteocytes
4. osteoprogenitor cells

D

Which of the following are found in compact bone and cancellous bone?

1. Haversian systems
2. Haversian canals
3. lamellae
4. lacunae

C

Which of the following are *only* found in cancellous bone?

1. canaliculi
2. Volkmann’s canals

3. trabeculae
4. calcium salts

C

The area of a bone where the nutrient foramen passes forms what kind of bone marking?

1. a hole
2. a facet
3. a canal
4. a fissure

A

Critical Thinking Questions

If the articular cartilage at the end of one of your long bones were to degenerate, what symptoms do you think you would experience? Why?

If the articular cartilage at the end of one of your long bones were to deteriorate, which is actually what happens in osteoarthritis, you

would experience joint pain at the end of that bone and limitation of motion at that joint because there would be no cartilage to reduce friction between adjacent bones and there would be no cartilage to act as a shock absorber.

In what ways is the structural makeup of compact and spongy bone well suited to their respective functions?

The densely packed concentric rings of matrix in compact bone are ideal for resisting compressive forces, which is the function of compact bone. The open spaces of the trabeculated network of spongy bone allow spongy bone to support shifts in weight distribution, which is the function of spongy bone.

Glossary

articular cartilage
: thin layer of cartilage covering an epiphysis; reduces friction and acts as a shock absorber

articulation
: where two bone surfaces meet

canaliculi

(singular = canaliculus) channels within the bone matrix that house one of an osteocyte’s many cytoplasmic extensions that it uses to communicate and receive nutrients

central canal

longitudinal channel in the center of each osteon; contains blood vessels, nerves, and lymphatic vessels; also known as the Haversian canal

compact bone

dense osseous tissue that can withstand compressive forces

diaphysis

tubular shaft that runs between the proximal and distal ends of a long bone

diploë

layer of spongy bone, that is sandwiched between two the layers of compact bone found in flat bones

endosteum

delicate membranous lining of a bone’s medullary cavity

epiphyseal plate

(also, growth plate) sheet of hyaline cartilage in the metaphysis of an immature bone;

replaced by bone tissue as the organ grows in length

epiphysis
: wide section at each end of a long bone; filled with spongy bone and red marrow

hole
: opening or depression in a bone

lacunae
: (singular = lacuna) spaces in a bone that house an osteocyte

medullary cavity
: hollow region of the diaphysis; filled with yellow marrow

nutrient foramen
: small opening in the middle of the external surface of the diaphysis, through which an artery enters the bone to provide nourishment

osteoblast
: cell responsible for forming new bone

osteoclast
: cell responsible for resorbing bone

osteocyte
: primary cell in mature bone; responsible for maintaining the matrix

osteogenic cell
: undifferentiated cell with high mitotic activity; the only bone cells that divide; they differentiate and develop into osteoblasts

osteon
: (also, Haversian system) basic structural unit of compact bone; made of concentric layers of calcified matrix

perforating canal
: (also, Volkmann’s canal) channel that branches off from the central canal and houses vessels and nerves that extend to the periosteum and endosteum

periosteum
: fibrous membrane covering the outer surface of bone and continuous with ligaments

projection
: bone markings where part of the surface sticks out above the rest of the surface, where tendons and ligaments attach

spongy bone
: (also, cancellous bone) trabeculated osseous tissue that supports shifts in weight distribution

trabeculae
: (singular = trabecula) spikes or sections of

the lattice-like matrix in spongy bone

Exercise, Nutrition, Hormones, and Bone Tissue
By the end of this section, you will be able to:

- Describe the effect exercise has on bone tissue
- List the nutrients that affect bone health
- Discuss the role those nutrients play in bone health
- Describe the effects of hormones on bone tissue

All of the organ systems of your body are interdependent, and the skeletal system is no exception. The food you take in via your digestive system and the hormones secreted by your endocrine system affect your bones. Even using your muscles to engage in exercise has an impact on your bones.

Exercise and Bone Tissue

During long space missions, astronauts can lose approximately 1 to 2 percent of their bone mass per month. This loss of bone mass is thought to be caused by the lack of mechanical stress on astronauts' bones due to the low gravitational forces in space. Lack of mechanical stress causes bones to lose mineral salts and collagen fibers, and thus strength. Similarly, mechanical stress stimulates the deposition of mineral salts and collagen fibers. The internal and external structure of a bone will change

as stress increases or decreases so that the bone is an ideal size and weight for the amount of activity it endures. That is why people who exercise regularly have thicker bones than people who are more sedentary. It is also why a broken bone in a cast atrophies while its contralateral mate maintains its concentration of mineral salts and collagen fibers. The bones undergo remodeling as a result of forces (or lack of forces) placed on them.

Numerous, controlled studies have demonstrated that people who exercise regularly have greater bone density than those who are more sedentary. Any type of exercise will stimulate the deposition of more bone tissue, but resistance training has a greater effect than cardiovascular activities. Resistance training is especially important to slow down the eventual bone loss due to aging and for preventing osteoporosis.

Nutrition and Bone Tissue

The vitamins and minerals contained in all of the food we consume are important for all of our organ systems. However, there are certain nutrients that affect bone health.

Calcium and Vitamin D

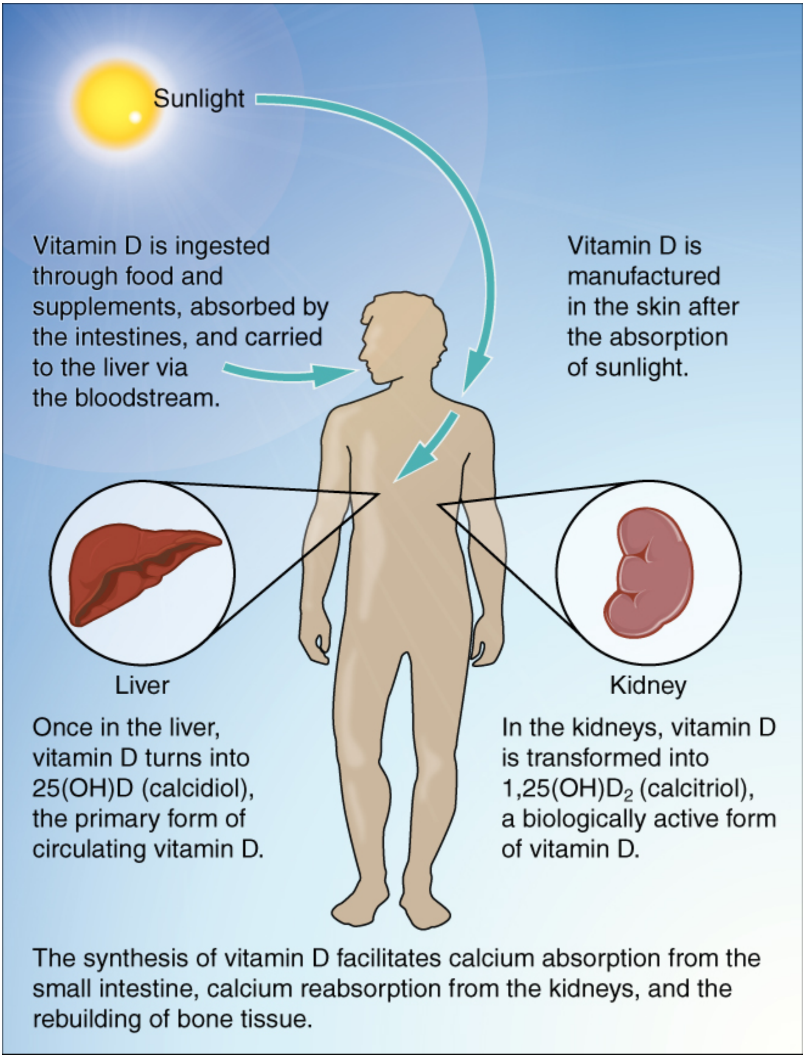
You already know that calcium is a critical component of bone, especially in the form of calcium phosphate and calcium carbonate. Since the body cannot make calcium, it must be obtained from the diet. However, calcium cannot be absorbed from the small intestine without vitamin D. Therefore, intake of vitamin D is also critical to bone health. In addition to vitamin D’s role in calcium absorption, it also plays a role, though not as clearly understood, in bone remodeling.

Milk and other dairy foods are not the only sources of calcium. This important nutrient is also found in green leafy vegetables, broccoli, and intact salmon and canned sardines with their soft bones. Nuts, beans, seeds, and shellfish provide calcium in smaller quantities.

Except for fatty fish like salmon and tuna, or fortified milk or cereal, vitamin D is not found naturally in many foods. The action of sunlight on the skin triggers the body to produce its own vitamin D ([link]), but many people, especially those of darker complexion and those living in northern latitudes where the sun’s rays are not as strong, are deficient in vitamin D. In cases of deficiency, a doctor can prescribe a vitamin D supplement.

Synthesis of Vitamin D

Sunlight is one source of vitamin D.



Other Nutrients

Vitamin K also supports bone mineralization and may have a synergistic role with vitamin D in the regulation of bone growth. Green leafy vegetables are a good source of vitamin K.

The minerals magnesium and fluoride may also play a role in supporting bone health. While magnesium is only found in trace amounts in the human body, more than 60 percent of it is in the skeleton, suggesting it plays a role in the structure of bone. Fluoride can displace the hydroxyl group in bone's hydroxyapatite crystals and form fluorapatite. Similar to its effect on dental enamel, fluorapatite helps stabilize and strengthen bone mineral. Fluoride can also enter spaces within hydroxyapatite crystals, thus increasing their density.

Omega-3 fatty acids have long been known to reduce inflammation in various parts of the body. Inflammation can interfere with the function of osteoblasts, so consuming omega-3 fatty acids, in the diet or in supplements, may also help enhance production of new osseous tissue. [link] summarizes the role of nutrients in bone health.

Nutrients and Bone Health

Nutrient	Role in bone health
Calcium	Needed to make calcium phosphate and calcium carbonate, which form the hydroxyapatite

	crystals that give bone its hardness
Vitamin D	Needed for calcium absorption
Vitamin K	Supports bone mineralization; may have synergistic effect with vitamin D
Magnesium	Structural component of bone
Fluoride	Structural component of bone
Omega-3 fatty acids	Reduces inflammation that may interfere with osteoblast function

Hormones and Bone Tissue

The endocrine system produces and secretes hormones, many of which interact with the skeletal system. These hormones are involved in controlling bone growth, maintaining bone once it is formed, and remodeling it.

Hormones That Influence Osteoblasts and/or Maintain the Matrix

Several hormones are necessary for controlling bone

growth and maintaining the bone matrix. The pituitary gland secretes growth hormone (GH), which, as its name implies, controls bone growth in several ways. It triggers chondrocyte proliferation in epiphyseal plates, resulting in the increasing length of long bones. GH also increases calcium retention, which enhances mineralization, and stimulates osteoblastic activity, which improves bone density.

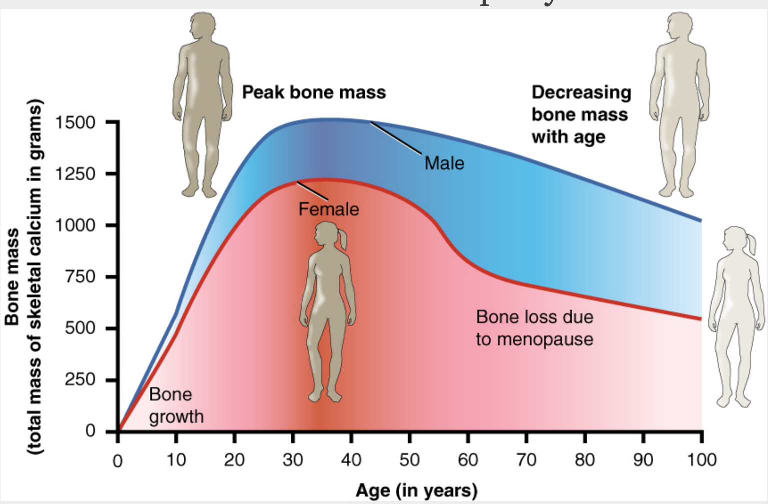
GH is not alone in stimulating bone growth and maintaining osseous tissue. Thyroxine, a hormone secreted by the thyroid gland promotes osteoblastic activity and the synthesis of bone matrix. During puberty, the sex hormones (estrogen in girls, testosterone in boys) also come into play. They too promote osteoblastic activity and production of bone matrix, and in addition, are responsible for the growth spurt that often occurs during adolescence. They also promote the conversion of the epiphyseal plate to the epiphyseal line (i.e., cartilage to its bony remnant), thus bringing an end to the longitudinal growth of bones. Additionally, calcitriol, the active form of vitamin D, is produced by the kidneys and stimulates the absorption of calcium and phosphate from the digestive tract.

Aging and the…
Skeletal System
Osteoporosis is a disease characterized by a

decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation, a common occurrence as the body ages. Notice how this is different from Paget's disease. In Paget's disease, new bone is formed in an attempt to keep up with the resorption by the overactive osteoclasts, but that new bone is produced haphazardly. In fact, when a physician is evaluating a patient with thinning bone, he or she will test for osteoporosis and Paget's disease (as well as other diseases). Osteoporosis does not have the elevated blood levels of alkaline phosphatase found in Paget's disease.

Graph Showing Relationship Between Age and Bone Mass

Bone density peaks at about 30 years of age. Women lose bone mass more rapidly than men.



While osteoporosis can involve any bone, it most commonly affects the proximal ends of the femur, vertebrae, and wrist. As a result of the loss of bone

density, the osseous tissue may not provide adequate support for everyday functions, and something as simple as a sneeze can cause a vertebral fracture. When an elderly person falls and breaks a hip (really, the femur), it is very likely the femur that broke first, which resulted in the fall. Histologically, osteoporosis is characterized by a reduction in the thickness of compact bone and the number and size of trabeculae in cancellous bone.
[link] shows that women lose bone mass more quickly than men starting at about 50 years of age. This occurs because 50 is the approximate age at which women go through menopause. Not only do their menstrual periods lessen and eventually cease, but their ovaries reduce in size and then cease the production of estrogen, a hormone that promotes osteoblastic activity and production of bone matrix. Thus, osteoporosis is more common in women than in men, but men can develop it, too. Anyone with a family history of osteoporosis has a greater risk of developing the disease, so the best treatment is prevention, which should start with a childhood diet that includes adequate intake of calcium and vitamin D and a lifestyle that includes weight-bearing exercise. These actions, as discussed above, are important in building bone mass. Promoting proper nutrition and weight-bearing exercise early in life can maximize bone mass before the age of 30, thus reducing the risk of osteoporosis.

For many elderly people, a hip fracture can be life

threatening. The fracture itself may not be serious, but the immobility that comes during the healing process can lead to the formation of blood clots that can lodge in the capillaries of the lungs, resulting in respiratory failure; pneumonia due to the lack of poor air exchange that accompanies immobility; pressure sores (bed sores) that allow pathogens to enter the body and cause infections; and urinary tract infections from catheterization. Current treatments for managing osteoporosis include bisphosphonates (the same medications often used in Paget's disease), calcitonin, and estrogen (for women only). Minimizing the risk of falls, for example, by removing tripping hazards, is also an important step in managing the potential outcomes from the disease.

Hormones That Influence Osteoclasts

Bone modeling and remodeling require osteoclasts to resorb unneeded, damaged, or old bone, and osteoblasts to lay down new bone. Two hormones that affect the osteoclasts are parathyroid hormone (PTH) and calcitonin.

PTH stimulates osteoclast proliferation and activity. As a result, calcium is released from the bones into the circulation, thus increasing the calcium ion concentration in the blood. PTH also promotes the

reabsorption of calcium by the kidney tubules, which can affect calcium homeostasis (see below).

The small intestine is also affected by PTH, albeit indirectly. Because another function of PTH is to stimulate the synthesis of vitamin D, and because vitamin D promotes intestinal absorption of calcium, PTH indirectly increases calcium uptake by the small intestine. Calcitonin, a hormone secreted by the thyroid gland, has some effects that counteract those of PTH. Calcitonin inhibits osteoclast activity and stimulates calcium uptake by the bones, thus reducing the concentration of calcium ions in the blood. As evidenced by their opposing functions in maintaining calcium homeostasis, PTH and calcitonin are generally *not* secreted at the same time. [link] summarizes the hormones that influence the skeletal system.

Hormones That Affect the Skeletal System

Hormone	Role
Growth hormone	Increases length of long bones, enhances mineralization, and improves bone density
Thyroxine	Stimulates bone growth

	and promotes synthesis of bone matrix
Sex hormones	Promote osteoblastic activity and production of bone matrix; responsible for adolescent growth spurt; promote conversion of epiphyseal plate to epiphyseal line
Calcitriol	Stimulates absorption of calcium and phosphate from digestive tract
Parathyroid hormone	Stimulates osteoclast proliferation and resorption of bone by osteoclasts; promotes reabsorption of calcium by kidney tubules; indirectly increases calcium absorption by small intestine
Calcitonin	Inhibits osteoclast activity and stimulates calcium uptake by bones

Chapter Review

Mechanical stress stimulates the deposition of mineral salts and collagen fibers within bones.

Calcium, the predominant mineral in bone, cannot be absorbed from the small intestine if vitamin D is lacking. Vitamin K supports bone mineralization and may have a synergistic role with vitamin D. Magnesium and fluoride, as structural elements, play a supporting role in bone health. Omega-3 fatty acids reduce inflammation and may promote production of new osseous tissue. Growth hormone increases the length of long bones, enhances mineralization, and improves bone density. Thyroxine stimulates bone growth and promotes the synthesis of bone matrix. The sex hormones (estrogen in women; testosterone in men) promote osteoblastic activity and the production of bone matrix, are responsible for the adolescent growth spurt, and promote closure of the epiphyseal plates. Osteoporosis is a disease characterized by decreased bone mass that is common in aging adults. Calcitriol stimulates the digestive tract to absorb calcium and phosphate. Parathyroid hormone (PTH) stimulates osteoclast proliferation and resorption of bone by osteoclasts. Vitamin D plays a synergistic role with PTH in stimulating the osteoclasts. Additional functions of PTH include promoting reabsorption of calcium by kidney tubules and indirectly increasing calcium absorption from the small intestine. Calcitonin inhibits osteoclast activity and stimulates calcium uptake by bones.

Review Questions

Wolff's law, which describes the effect of mechanical forces in bone modeling/remodeling, would predict that _____

1. a right-handed pitcher will have thicker bones in his right arm compared to his left.
2. a right-handed cyclist will have thicker bones in her right leg compared to her left.
3. a broken bone will heal thicker than it was before the fracture.
4. a bed-ridden patient will have thicker bones than an athlete.

A

Calcium cannot be absorbed from the small intestine if _____ is lacking.

1. vitamin D
2. vitamin K
3. calcitonin
4. fluoride

A

Which one of the following foods is best for bone health?

1. carrots
2. liver
3. leafy green vegetables
4. oranges

C

Which of the following hormones are responsible for the adolescent growth spurt?

1. estrogen and testosterone
2. calcitonin and calcitriol
3. growth hormone and parathyroid hormone
4. thyroxine and progesterone

A

With respect to their direct effects on osseous tissue, which pair of hormones has actions that oppose each other?

1. estrogen and testosterone
2. calcitonin and calcitriol
3. estrogen and progesterone
4. calcitonin and parathyroid hormone

D

Critical Thinking Questions

If you were a dietician who had a young female patient with a family history of osteoporosis, what foods would you suggest she include in her diet? Why?

Since maximum bone mass is achieved by age 30, I would want this patient to have adequate calcium and vitamin D in her diet. To do this, I would recommend ingesting milk and other dairy foods, green leafy vegetables, and intact canned sardines so she receives sufficient calcium. Intact salmon would be a good source for calcium and vitamin D. Other fatty fish would also be a good vitamin D source.

During the early years of space exploration our astronauts, who had been floating in space, would return to earth showing significant bone loss dependent on how long they were in space. Discuss how this might happen and what could be done to alleviate this condition.

Astronauts floating in space were not exerting

significant pressure on their bones; they were "weightless." Without the force of gravity exerting pressure on the bones, bone mass was lost. To alleviate this condition, astronauts now do resistive exercise designed to apply forces to the bones and thus help keep them healthy.

Glossary

osteoporosis
: disease characterized by a decrease in bone mass; occurs when the rate of bone resorption exceeds the rate of bone formation, a common occurrence as the body ages

Calcium Homeostasis: Interactions of the Skeletal System and Other Organ Systems

By the end of this section, you will be able to:

- Describe the effect of too much or too little calcium on the body
- Explain the process of calcium homeostasis

Calcium is not only the most abundant mineral in bone, it is also the most abundant mineral in the human body. Calcium ions are needed not only for bone mineralization but for tooth health, regulation of the heart rate and strength of contraction, blood coagulation, contraction of smooth and skeletal muscle cells, and regulation of nerve impulse conduction. The normal level of calcium in the blood is about 10 mg/dL. When the body cannot maintain this level, a person will experience hypo- or hypercalcemia.

Hypocalcemia, a condition characterized by abnormally low levels of calcium, can have an adverse effect on a number of different body systems including circulation, muscles, nerves, and bone. Without adequate calcium, blood has difficulty coagulating, the heart may skip beats or stop beating altogether, muscles may have difficulty contracting, nerves may have difficulty functioning, and bones may become brittle. The causes of hypocalcemia can range from hormonal imbalances to an improper diet. Treatments vary according to

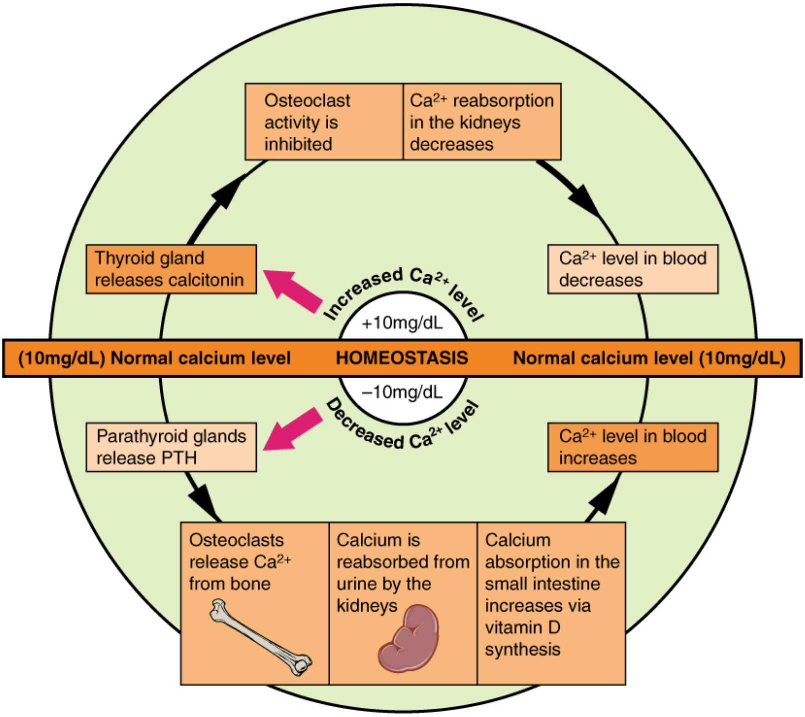
the cause, but prognoses are generally good.

Conversely, in **hypercalcemia**, a condition characterized by abnormally high levels of calcium, the nervous system is underactive, which results in lethargy, sluggish reflexes, constipation and loss of appetite, confusion, and in severe cases, coma.

Obviously, calcium homeostasis is critical. The skeletal, endocrine, and digestive systems play a role in this, but the kidneys do, too. These body systems work together to maintain a normal calcium level in the blood ([link]).

Pathways in Calcium Homeostasis

The body regulates calcium homeostasis with two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated.



Calcium is a chemical element that cannot be produced by any biological processes. The only way it can enter the body is through the diet. The bones act as a storage site for calcium: The body deposits calcium in the bones when blood levels get too high, and it releases calcium when blood levels drop too low. This process is regulated by PTH, vitamin D, and calcitonin.

Cells of the parathyroid gland have plasma membrane receptors for calcium. When calcium is not binding to these receptors, the cells release PTH, which stimulates osteoclast proliferation and resorption of bone by osteoclasts. This

demineralization process releases calcium into the blood. PTH promotes reabsorption of calcium from the urine by the kidneys, so that the calcium returns to the blood. Finally, PTH stimulates the synthesis of vitamin D, which in turn, stimulates calcium absorption from any digested food in the small intestine.

When all these processes return blood calcium levels to normal, there is enough calcium to bind with the receptors on the surface of the cells of the parathyroid glands, and this cycle of events is turned off ([link]).

When blood levels of calcium get too high, the thyroid gland is stimulated to release calcitonin ([link]), which inhibits osteoclast activity and stimulates calcium uptake by the bones, but also decreases reabsorption of calcium by the kidneys. All of these actions lower blood levels of calcium. When blood calcium levels return to normal, the thyroid gland stops secreting calcitonin.

Chapter Review

Calcium homeostasis, i.e., maintaining a blood calcium level of about 10 mg/dL, is critical for normal body functions. Hypocalcemia can result in problems with blood coagulation, muscle contraction, nerve functioning, and bone strength.

Hypercalcemia can result in lethargy, sluggish reflexes, constipation and loss of appetite, confusion, and coma. Calcium homeostasis is controlled by PTH, vitamin D, and calcitonin and the interactions of the skeletal, endocrine, digestive, and urinary systems.

Review Questions

When calcium levels are too high or too low, which body system is primarily affected?

1. skeletal system
2. endocrine system
3. digestive system
4. nervous system

D

All of the following play a role in calcium homeostasis except

1. thyroxine
2. calcitonin
3. parathyroid hormone
4. vitamin D

A

Which of the following is most likely to be released when blood calcium levels are elevated?

1. thyroxine
2. calcitonin
3. parathyroid hormone
4. vitamin D

B

Critical Thinking Questions

An individual with very low levels of vitamin D presents themselves to you complaining of seemingly fragile bones. Explain how these might be connected.

Vitamin D is required for calcium absorption by the gut. Low vitamin D could lead to insufficient levels of calcium in the blood so the calcium is being released from the bones. The reduction of calcium from the bones can make

them weak and subject to fracture.

Describe the effects caused when the parathyroid gland fails to respond to calcium bound to its receptors.

Under "normal" conditions, receptors in the parathyroid glands bind blood calcium. When the receptors are full, the parathyroid gland stops secreting PTH. In the condition described, the parathyroid glands are not responding to the signal that there is sufficient calcium in the blood and they keep releasing PTH, which causes the bone to release more calcium into the blood. Ultimately, the bones become fragile and hypercalcemia can result.

Glossary

hypercalcemia
: condition characterized by abnormally high levels of calcium

hypocalcemia
: condition characterized by abnormally low levels of calcium

Introduction

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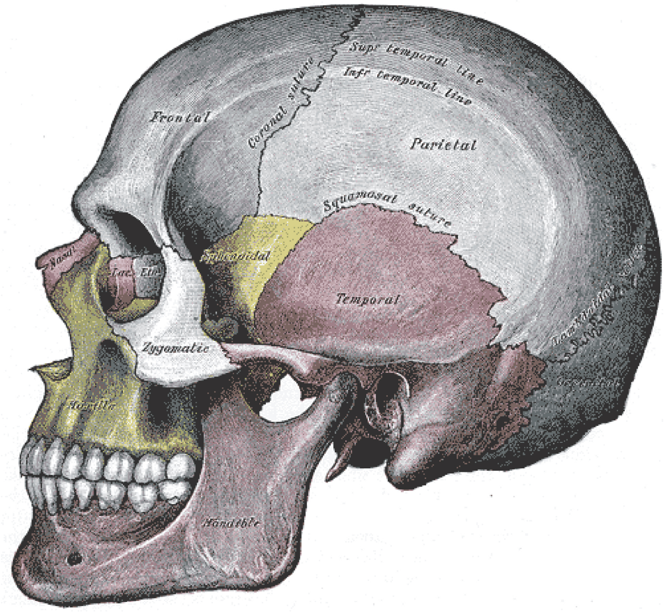
Lateral View of the Human Skull



Chapter Objectives

After studying this chapter, you will be able to:

- Describe the functions of the skeletal system and define its two major subdivisions
- Identify the bones and bony structures of the skull, the cranial suture lines, the cranial fossae, and the openings in the skull
- Discuss the vertebral column and regional variations in its bony components and

curvatures
- Describe the components of the thoracic cage
- Discuss the embryonic development of the axial skeleton

The skeletal system forms the rigid internal framework of the body. It consists of the bones, cartilages, and ligaments. Bones support the weight of the body, allow for body movements, and protect internal organs. Cartilage provides flexible strength and support for body structures such as the thoracic cage, the external ear, and the trachea and larynx. At joints of the body, cartilage can also unite adjacent bones or provide cushioning between them. Ligaments are the strong connective tissue bands that hold the bones at a moveable joint together and serve to prevent excessive movements of the joint that would result in injury. Providing movement of the skeleton are the muscles of the body, which are firmly attached to the skeleton via connective tissue structures called tendons. As muscles contract, they pull on the bones to produce movements of the body. Thus, without a skeleton, you would not be able to stand, run, or even feed yourself!

Each bone of the body serves a particular function, and therefore bones vary in size, shape, and strength based on these functions. For example, the bones of

the lower back and lower limb are thick and strong to support your body weight. Similarly, the size of a bony landmark that serves as a muscle attachment site on an individual bone is related to the strength of this muscle. Muscles can apply very strong pulling forces to the bones of the skeleton. To resist these forces, bones have enlarged bony landmarks at sites where powerful muscles attach. This means that not only the size of a bone, but also its shape, is related to its function. For this reason, the identification of bony landmarks is important during your study of the skeletal system.

Bones are also dynamic organs that can modify their strength and thickness in response to changes in muscle strength or body weight. Thus, muscle attachment sites on bones will thicken if you begin a workout program that increases muscle strength. Similarly, the walls of weight-bearing bones will thicken if you gain body weight or begin pounding the pavement as part of a new running regimen. In contrast, a reduction in muscle strength or body weight will cause bones to become thinner. This may happen during a prolonged hospital stay, following limb immobilization in a cast, or going into the weightlessness of outer space. Even a change in diet, such as eating only soft food due to the loss of teeth, will result in a noticeable decrease in the size and thickness of the jaw bones.

Divisions of the Skeletal System

By the end of this section, you will be able to:

- Discuss the functions of the skeletal system
- Distinguish between the axial skeleton and appendicular skeleton
- Define the axial skeleton and its components
- Define the appendicular skeleton and its components

The skeletal system includes all of the bones, cartilages, and ligaments of the body that support and give shape to the body and body structures. The **skeleton** consists of the bones of the body. For adults, there are 206 bones in the skeleton. Younger individuals have higher numbers of bones because some bones fuse together during childhood and adolescence to form an adult bone. The primary functions of the skeleton are to provide a rigid, internal structure that can support the weight of the body against the force of gravity, and to provide a structure upon which muscles can act to produce movements of the body. The lower portion of the skeleton is specialized for stability during walking or running. In contrast, the upper skeleton has greater mobility and ranges of motion, features that allow you to lift and carry objects or turn your head and trunk.

In addition to providing for support and movements of the body, the skeleton has protective and storage

functions. It protects the internal organs, including the brain, spinal cord, heart, lungs, and pelvic organs. The bones of the skeleton serve as the primary storage site for important minerals such as calcium and phosphate. The bone marrow found within bones stores fat and houses the blood-cell producing tissue of the body.

The skeleton is subdivided into two major divisions—the axial and appendicular.

The Axial Skeleton

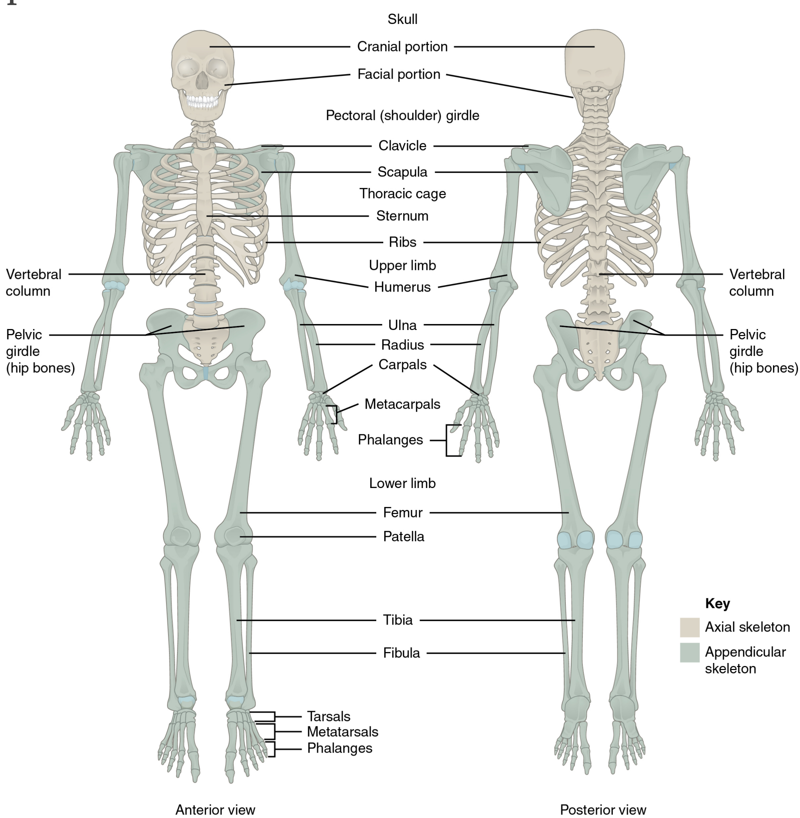
The skeleton is subdivided into two major divisions—the axial and appendicular. The **axial skeleton** forms the vertical, central axis of the body and includes all bones of the head, neck, chest, and back ([link]). It serves to protect the brain, spinal cord, heart, and lungs. It also serves as the attachment site for muscles that move the head, neck, and back, and for muscles that act across the shoulder and hip joints to move their corresponding limbs.

The axial skeleton of the adult consists of 80 bones, including the **skull**, the **vertebral column**, and the **thoracic cage**. The skull is formed by 22 bones. Also associated with the head are an additional seven bones, including the **hyoid bone** and the **ear ossicles** (three small bones found in each middle ear). The vertebral column consists of 24 bones,

each called a **vertebra**, plus the **sacrum** and **coccyx**. The thoracic cage includes the 12 pairs of **ribs**, and the **sternum**, the flattened bone of the anterior chest.

Axial and Appendicular Skeleton

The axial skeleton supports the head, neck, back, and chest and thus forms the vertical axis of the body. It consists of the skull, vertebral column (including the sacrum and coccyx), and the thoracic cage, formed by the ribs and sternum. The appendicular skeleton is made up of all bones of the upper and lower limbs.



The Appendicular Skeleton

The **appendicular skeleton** includes all bones of the upper and lower limbs, plus the bones that attach each limb to the axial skeleton. There are 126 bones in the appendicular skeleton of an adult. The bones of the appendicular skeleton are covered in a separate chapter.

Chapter Review

The skeletal system includes all of the bones, cartilages, and ligaments of the body. It serves to support the body, protect the brain and other internal organs, and provides a rigid structure upon which muscles can pull to generate body movements. It also stores fat and the tissue responsible for the production of blood cells. The skeleton is subdivided into two parts. The axial skeleton forms a vertical axis that includes the head, neck, back, and chest. It has 80 bones and consists of the skull, vertebral column, and thoracic cage. The adult vertebral column consists of 24 vertebrae plus the sacrum and coccyx. The thoracic cage is formed by 12 pairs of ribs and the sternum. The appendicular skeleton consists of 126 bones in the adult and includes all of the bones of the upper and lower limbs plus the bones that anchor each limb to the axial skeleton.

Review Questions

Which of the following is part of the axial skeleton?

1. shoulder bones
2. thigh bone
3. foot bones
4. vertebral column

D

Which of the following is a function of the axial skeleton?

1. allows for movement of the wrist and hand
2. protects nerves and blood vessels at the elbow
3. supports trunk of body
4. allows for movements of the ankle and foot

C

The axial skeleton _____.

1. consists of 126 bones
2. forms the vertical axis of the body

3. includes all bones of the body trunk and limbs
4. includes only the bones of the lower limbs

B

Critical Thinking Question

Define the two divisions of the skeleton.

The axial skeleton forms the vertical axis of the body and includes the bones of the head, neck, back, and chest of the body. It consists of 80 bones that include the skull, vertebral column, and thoracic cage. The appendicular skeleton consists of 126 bones and includes all bones of the upper and lower limbs.

Discuss the functions of the axial skeleton.

The axial skeleton supports the head, neck, back, and chest of the body and allows for movements of these body regions. It also gives bony protections for the brain, spinal cord, heart, and lungs; stores fat and minerals; and

houses the blood-cell producing tissue.

Glossary

appendicular skeleton
: all bones of the upper and lower limbs, plus the girdle bones that attach each limb to the axial skeleton

axial skeleton
: central, vertical axis of the body, including the skull, vertebral column, and thoracic cage

coccyx
: small bone located at inferior end of the adult vertebral column that is formed by the fusion of four coccygeal vertebrae; also referred to as the “tailbone”

ear ossicles
: three small bones located in the middle ear cavity that serve to transmit sound vibrations to the inner ear

hyoid bone
: small, U-shaped bone located in upper neck that does not contact any other bone

ribs
: thin, curved bones of the chest wall

sacrum
: single bone located near the inferior end of the adult vertebral column that is formed by the fusion of five sacral vertebrae; forms the posterior portion of the pelvis

skeleton
: bones of the body

skull
: bony structure that forms the head, face, and jaws, and protects the brain; consists of 22 bones

sternum
: flattened bone located at the center of the anterior chest

thoracic cage
: consists of 12 pairs of ribs and sternum

vertebra
: individual bone in the neck and back regions of the vertebral column

vertebral column
: entire sequence of bones that extend from the skull to the tailbone

The Vertebral Column

By the end of this section, you will be able to:

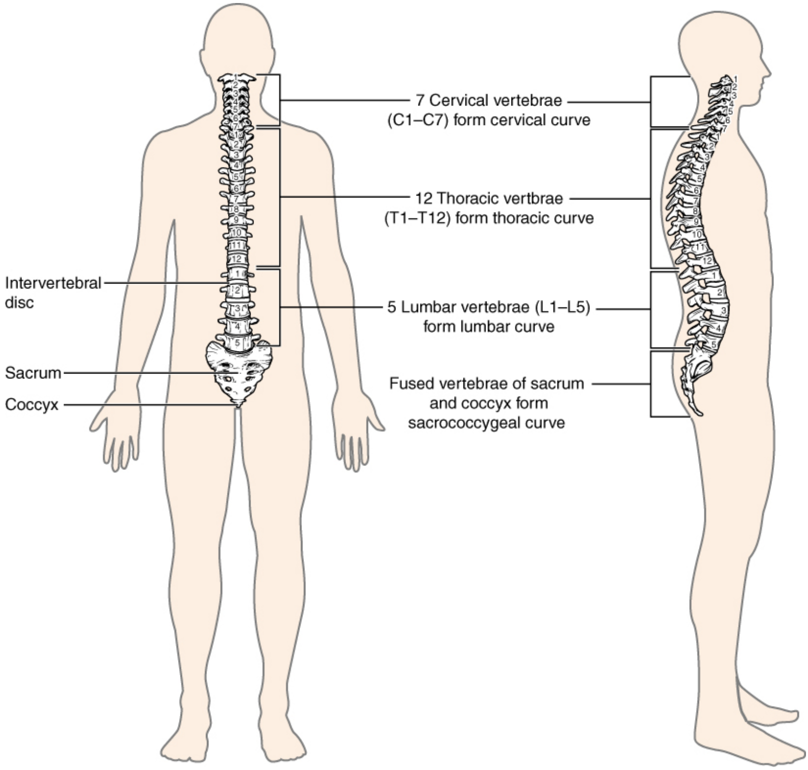
- Describe each region of the vertebral column and the number of bones in each region
- Discuss the curves of the vertebral column and how these change after birth
- Describe a typical vertebra and determine the distinguishing characteristics for vertebrae in each vertebral region and features of the sacrum and the coccyx
- Define the structure of an intervertebral disc
- Determine the location of the ligaments that provide support for the vertebral column

The vertebral column is also known as the spinal column or spine ([link]). It consists of a sequence of vertebrae (singular = vertebra), each of which is separated and united by an **intervertebral disc**. Together, the vertebrae and intervertebral discs form the vertebral column. It is a flexible column that supports the head, neck, and body and allows for their movements. It also protects the spinal cord, which passes down the back through openings in the vertebrae.

Vertebral Column

The adult vertebral column consists of 24 vertebrae, plus the sacrum and coccyx. The vertebrae are divided into three regions: cervical C1–C7 vertebrae, thoracic T1–T12 vertebrae, and lumbar L1–L5 vertebrae. The vertebral column is curved, with two

primary curvatures (thoracic and sacrococcygeal curves) and two secondary curvatures (cervical and lumbar curves).



Regions of the Vertebral Column

The vertebral column originally develops as a series of 33 vertebrae, but this number is eventually reduced to 24 vertebrae, plus the sacrum and coccyx. The vertebral column is subdivided into five regions, with the vertebrae in each area named for that region and numbered in descending order. In the neck, there are seven cervical vertebrae, each

designated with the letter “C” followed by its number. Superiorly, the C1 vertebra articulates (forms a joint) with the occipital condyles of the skull. Inferiorly, C1 articulates with the C2 vertebra, and so on. Below these are the 12 thoracic vertebrae, designated T1–T12. The lower back contains the L1–L5 lumbar vertebrae. The single sacrum, which is also part of the pelvis, is formed by the fusion of five sacral vertebrae. Similarly, the coccyx, or tailbone, results from the fusion of four small coccygeal vertebrae. However, the sacral and coccygeal fusions do not start until age 20 and are not completed until middle age.

An interesting anatomical fact is that almost all mammals have seven cervical vertebrae, regardless of body size. This means that there are large variations in the size of cervical vertebrae, ranging from the very small cervical vertebrae of a shrew to the greatly elongated vertebrae in the neck of a giraffe. In a full-grown giraffe, each cervical vertebra is 11 inches tall.

Curvatures of the Vertebral Column

The adult vertebral column does not form a straight line, but instead has four curvatures along its length (see [link]). These curves increase the vertebral column’s strength, flexibility, and ability to absorb shock. When the load on the spine is increased, by

carrying a heavy backpack for example, the curvatures increase in depth (become more curved) to accommodate the extra weight. They then spring back when the weight is removed. The four adult curvatures are classified as either primary or secondary curvatures. Primary curves are retained from the original fetal curvature, while secondary curvatures develop after birth.

During fetal development, the body is flexed anteriorly into the fetal position, giving the entire vertebral column a single curvature that is concave anteriorly. In the adult, this fetal curvature is retained in two regions of the vertebral column as the **thoracic curve**, which involves the thoracic vertebrae, and the **sacrococcygeal curve**, formed by the sacrum and coccyx. Each of these is thus called a **primary curve** because they are retained from the original fetal curvature of the vertebral column.

A **secondary curve** develops gradually after birth as the child learns to sit upright, stand, and walk. Secondary curves are concave posteriorly, opposite in direction to the original fetal curvature. The **cervical curve** of the neck region develops as the infant begins to hold their head upright when sitting. Later, as the child begins to stand and then to walk, the **lumbar curve** of the lower back develops. In adults, the lumbar curve is generally deeper in females.

Disorders associated with the curvature of the spine include **kyphosis** (an excessive posterior curvature of the thoracic region), **lordosis** (an excessive anterior curvature of the lumbar region), and **scoliosis** (an abnormal, lateral curvature, accompanied by twisting of the vertebral column).

Disorders of the...

Vertebral Column

Developmental anomalies, pathological changes, or obesity can enhance the normal vertebral column curves, resulting in the development of abnormal or excessive curvatures ([link]). Kyphosis, also referred to as humpback or hunchback, is an excessive posterior curvature of the thoracic region. This can develop when osteoporosis causes weakening and erosion of the anterior portions of the upper thoracic vertebrae, resulting in their gradual collapse ([link]). Lordosis, or swayback, is an excessive anterior curvature of the lumbar region and is most commonly associated with obesity or late pregnancy. The accumulation of body weight in the abdominal region results an anterior shift in the line of gravity that carries the weight of the body. This causes in an anterior tilt of the pelvis and a pronounced enhancement of the lumbar curve.

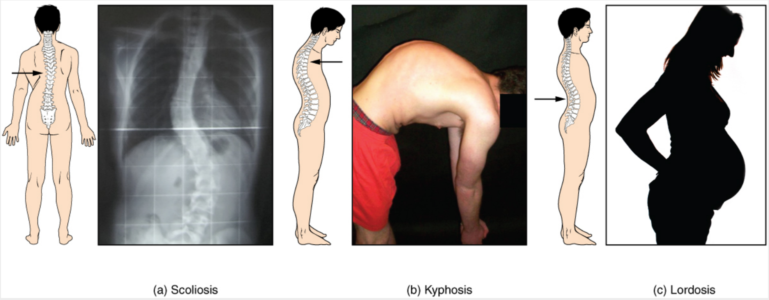
Scoliosis is an abnormal, lateral curvature, accompanied by twisting of the vertebral column.

Compensatory curves may also develop in other areas of the vertebral column to help maintain the head positioned over the feet. Scoliosis is the most common vertebral abnormality among girls. The cause is usually unknown, but it may result from weakness of the back muscles, defects such as differential growth rates in the right and left sides of the vertebral column, or differences in the length of the lower limbs. When present, scoliosis tends to get worse during adolescent growth spurts. Although most individuals do not require treatment, a back brace may be recommended for growing children. In extreme cases, surgery may be required.

Excessive vertebral curves can be identified while an individual stands in the anatomical position. Observe the vertebral profile from the side and then from behind to check for kyphosis or lordosis. Then have the person bend forward. If scoliosis is present, an individual will have difficulty in bending directly forward, and the right and left sides of the back will not be level with each other in the bent position.

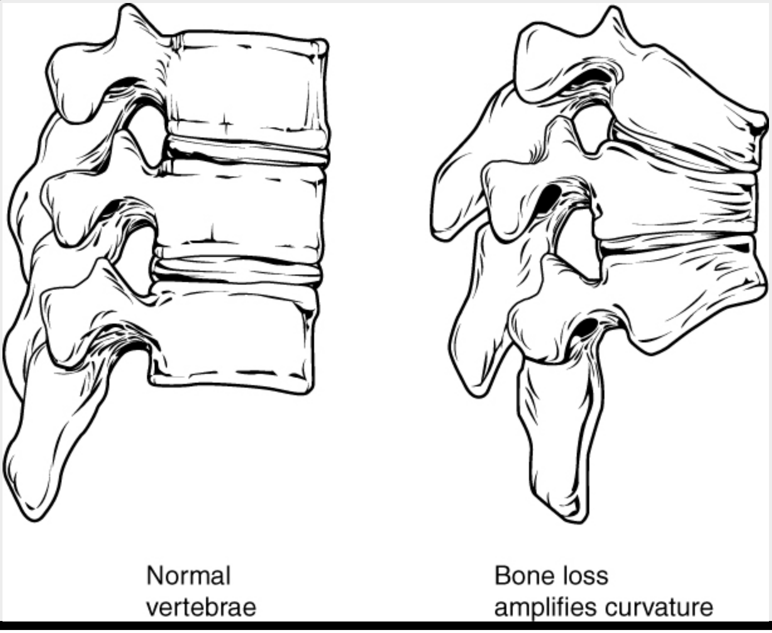
Abnormal Curvatures of the Vertebral Column

(a) Scoliosis is an abnormal lateral bending of the vertebral column. (b) An excessive curvature of the upper thoracic vertebral column is called kyphosis. (c) Lordosis is an excessive curvature in the lumbar region of the vertebral column.



Osteoporosis

Osteoporosis is an age-related disorder that causes the gradual loss of bone density and strength. When the thoracic vertebrae are affected, there can be a gradual collapse of the vertebrae. This results in kyphosis, an excessive curvature of the thoracic region.



Osteoporosis is a common age-related bone disease in which bone density and strength is decreased. Watch this video to get a better understanding of how thoracic vertebrae may become weakened and may fracture due to this disease. How may vertebral osteoporosis contribute to kyphosis?

General Structure of a Vertebra

Within the different regions of the vertebral column, vertebrae vary in size and shape, but they all follow a similar structural pattern. A typical vertebra will consist of a body, a vertebral arch, and seven processes ([link]).

The body is the anterior portion of each vertebra and is the part that supports the body weight. Because of this, the vertebral bodies progressively increase in size and thickness going down the vertebral column. The bodies of adjacent vertebrae are separated and strongly united by an

intervertebral disc.

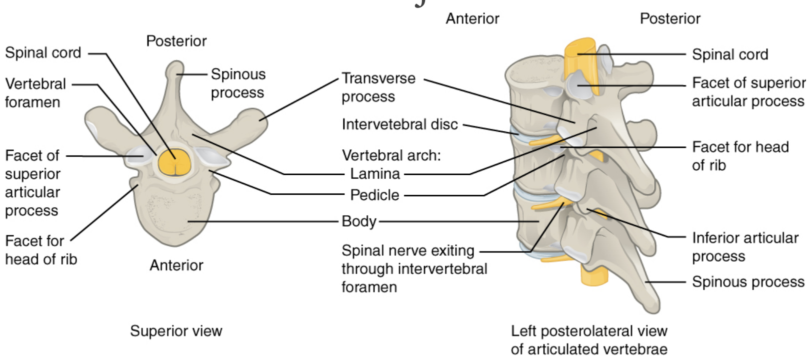
The **vertebral arch** forms the posterior portion of each vertebra. It consists of four parts, the right and left pedicles and the right and left laminae. Each **pedicle** forms one of the lateral sides of the vertebral arch. The pedicles are anchored to the posterior side of the vertebral body. Each **lamina** forms part of the posterior roof of the vertebral arch. The large opening between the vertebral arch and body is the **vertebral foramen**, which contains the spinal cord. In the intact vertebral column, the vertebral foramina of all of the vertebrae align to form the **vertebral (spinal) canal**, which serves as the bony protection and passageway for the spinal cord down the back. When the vertebrae are aligned together in the vertebral column, notches in the margins of the pedicles of adjacent vertebrae together form an **intervertebral foramen**, the opening through which a spinal nerve exits from the vertebral column ([link]).

Seven processes arise from the vertebral arch. Each paired **transverse process** projects laterally and arises from the junction point between the pedicle and lamina. The single **spinous process** (vertebral spine) projects posteriorly at the midline of the back. The vertebral spines can easily be felt as a series of bumps just under the skin down the middle of the back. The transverse and spinous processes serve as important muscle attachment sites. A

superior articular process extends or faces upward, and an **inferior articular process** faces or projects downward on each side of a vertebrae. The paired superior articular processes of one vertebra join with the corresponding paired inferior articular processes from the next higher vertebra. These junctions form slightly moveable joints between the adjacent vertebrae. The shape and orientation of the articular processes vary in different regions of the vertebral column and play a major role in determining the type and range of motion available in each region.

Parts of a Typical Vertebra

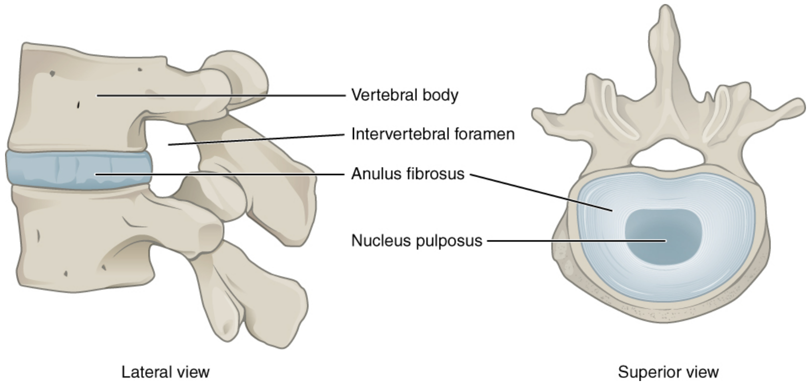
A typical vertebra consists of a body and a vertebral arch. The arch is formed by the paired pedicles and paired laminae. Arising from the vertebral arch are the transverse, spinous, superior articular, and inferior articular processes. The vertebral foramen provides for passage of the spinal cord. Each spinal nerve exits through an intervertebral foramen, located between adjacent vertebrae. Intervertebral discs unite the bodies of adjacent vertebrae.



Intervertebral Disc

The bodies of adjacent vertebrae are separated and

united by an intervertebral disc, which provides padding and allows for movements between adjacent vertebrae. The disc consists of a fibrous outer layer called the anulus fibrosus and a gel-like center called the nucleus pulposus. The intervertebral foramen is the opening formed between adjacent vertebrae for the exit of a spinal nerve.



Regional Modifications of Vertebrae

In addition to the general characteristics of a typical vertebra described above, vertebrae also display characteristic size and structural features that vary between the different vertebral column regions. Thus, cervical vertebrae are smaller than lumbar vertebrae due to differences in the proportion of body weight that each supports. Thoracic vertebrae have sites for rib attachment, and the vertebrae that give rise to the sacrum and coccyx have fused together into single bones.

Cervical Vertebrae

Typical **cervical vertebrae**, such as C4 or C5, have several characteristic features that differentiate them from thoracic or lumbar vertebrae ([link]). Cervical vertebrae have a small body, reflecting the fact that they carry the least amount of body weight. Cervical vertebrae usually have a bifid (Y-shaped) spinous process. The spinous processes of the C3–C6 vertebrae are short, but the spine of C7 is much longer. You can find these vertebrae by running your finger down the midline of the posterior neck until you encounter the prominent C7 spine located at the base of the neck. The transverse processes of the cervical vertebrae are sharply curved (U-shaped) to allow for passage of the cervical spinal nerves. Each transverse process also has an opening called the **transverse foramen**. An important artery that supplies the brain ascends up the neck by passing through these openings. The superior and inferior articular processes of the cervical vertebrae are flattened and largely face upward or downward, respectively.

The first and second cervical vertebrae are further modified, giving each a distinctive appearance. The first cervical (C1) vertebra is also called the **atlas**, because this is the vertebra that supports the skull on top of the vertebral column (in Greek mythology, Atlas was the god who supported the heavens on his shoulders). The C1 vertebra does not have a body or

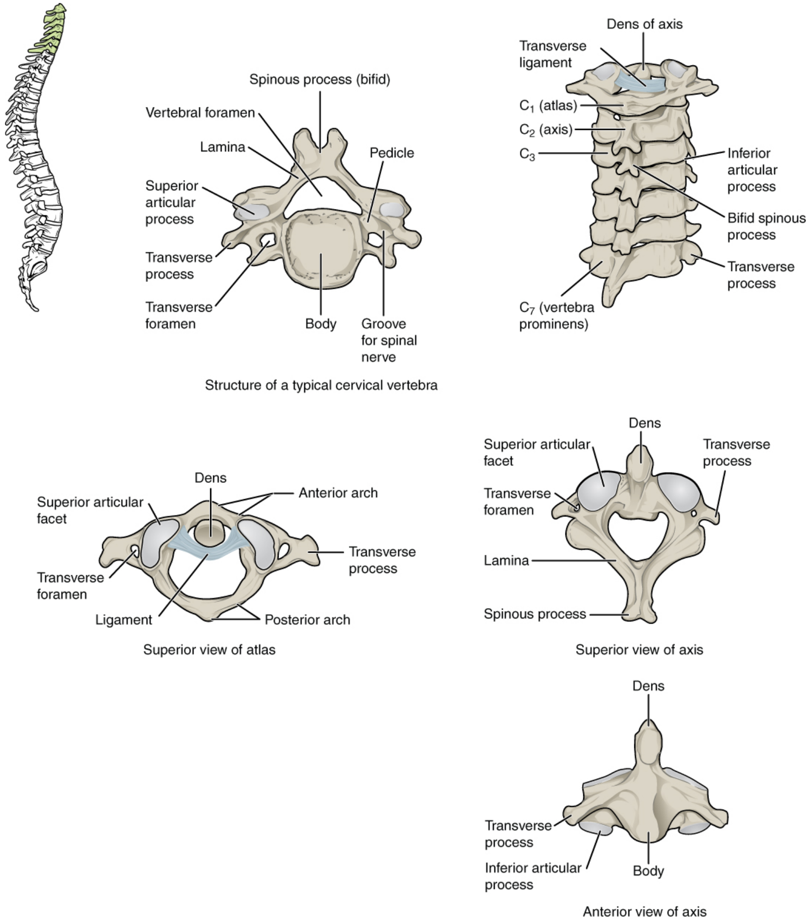
spinous process. Instead, it is ring-shaped, consisting of an **anterior arch** and a **posterior arch**. The transverse processes of the atlas are longer and extend more laterally than do the transverse processes of any other cervical vertebrae. The superior articular processes face upward and are deeply curved for articulation with the occipital condyles on the base of the skull. The inferior articular processes are flat and face downward to join with the superior articular processes of the C2 vertebra.

The second cervical (C2) vertebra is called the **axis**, because it serves as the axis for rotation when turning the head toward the right or left. The axis resembles typical cervical vertebrae in most respects, but is easily distinguished by the **dens** (odontoid process), a bony projection that extends upward from the vertebral body. The dens joins with the inner aspect of the anterior arch of the atlas, where it is held in place by transverse ligament.

Cervical Vertebrae

A typical cervical vertebra has a small body, a bifid spinous process, transverse processes that have a transverse foramen and are curved for spinal nerve passage. The atlas (C1 vertebra) does not have a body or spinous process. It consists of an anterior and a posterior arch and elongated transverse processes. The axis (C2 vertebra) has the upward projecting dens, which articulates with the anterior

arch of the atlas.



Thoracic Vertebrae

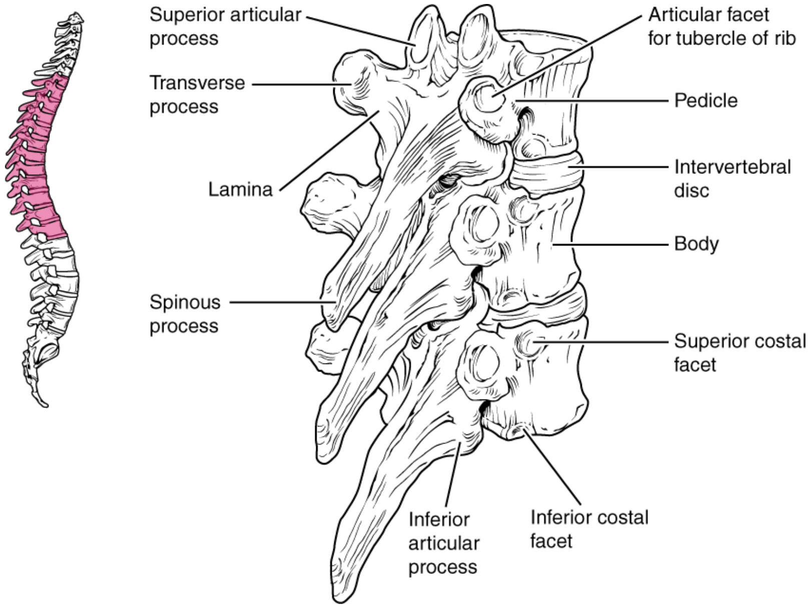
The bodies of the **thoracic vertebrae** are larger than those of cervical vertebrae ([link]). The characteristic feature for a typical midthoracic vertebra is the spinous process, which is long and has a pronounced downward angle that causes it to overlap the next inferior vertebra. The superior

articular processes of thoracic vertebrae face anteriorly and the inferior processes face posteriorly. These orientations are important determinants for the type and range of movements available to the thoracic region of the vertebral column.

Thoracic vertebrae have several additional articulation sites, each of which is called a **facet**, where a rib is attached. Most thoracic vertebrae have two facets located on the lateral sides of the body, each of which is called a **costal facet** (costal = “rib”). These are for articulation with the head (end) of a rib. An additional facet is located on the transverse process for articulation with the tubercle of a rib.

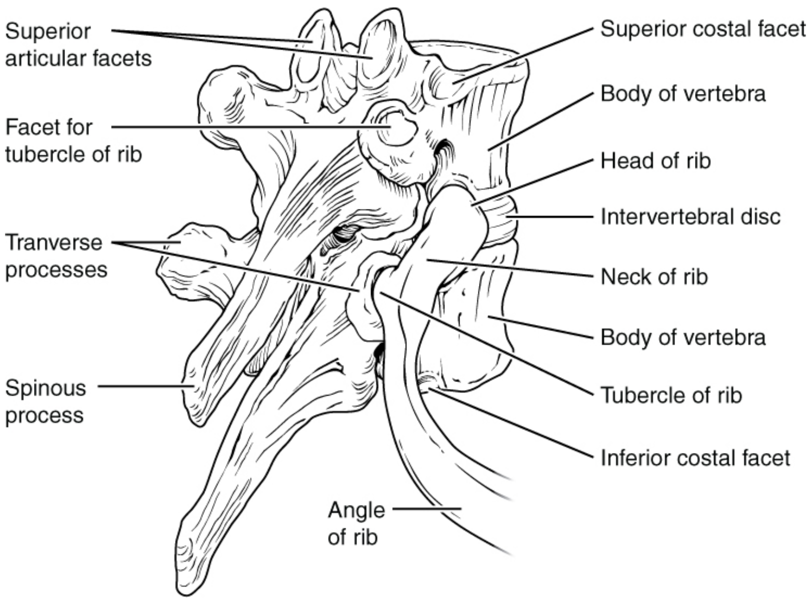
Thoracic Vertebrae

A typical thoracic vertebra is distinguished by the spinous process, which is long and projects downward to overlap the next inferior vertebra. It also has articulation sites (facets) on the vertebral body and a transverse process for rib attachment.



Rib Articulation in Thoracic Vertebrae

Thoracic vertebrae have superior and inferior articular facets on the vertebral body for articulation with the head of a rib, and a transverse process facet for articulation with the rib tubercle.

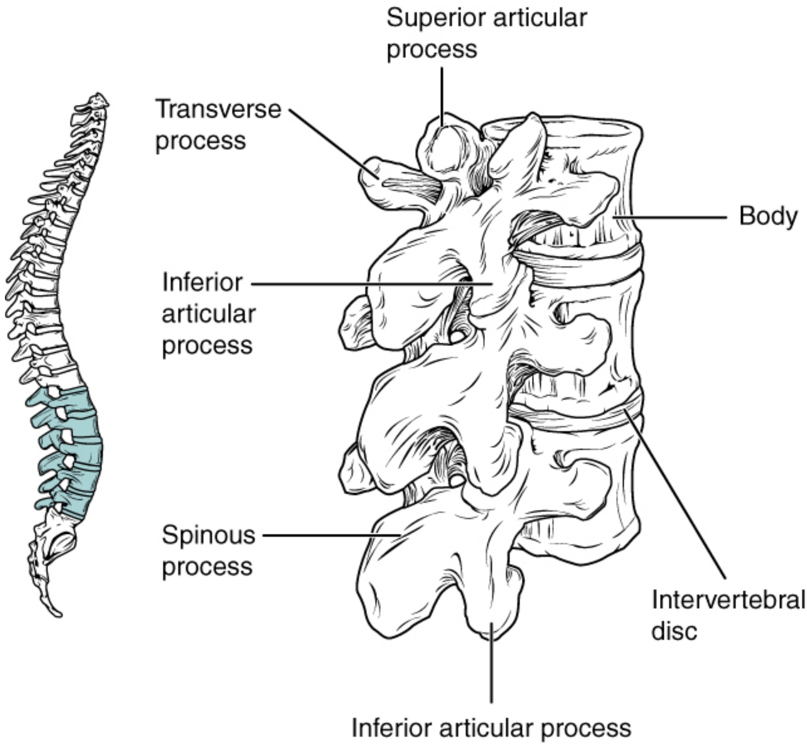


Lumbar Vertebrae

Lumbar vertebrae carry the greatest amount of body weight and are thus characterized by the large size and thickness of the vertebral body ([link]). They have short transverse processes and a short, blunt spinous process that projects posteriorly. The articular processes are large, with the superior process facing backward and the inferior facing forward.

Lumbar Vertebrae

Lumbar vertebrae are characterized by having a large, thick body and a short, rounded spinous process.



Sacrum and Coccyx

The sacrum is a triangular-shaped bone that is thick and wide across its superior base where it is weight bearing and then tapers down to an inferior, non-weight bearing apex ([link]). It is formed by the fusion of five sacral vertebrae, a process that does not begin until after the age of 20. On the anterior surface of the older adult sacrum, the lines of vertebral fusion can be seen as four transverse ridges. On the posterior surface, running down the midline, is the **median sacral crest**, a bumpy ridge that is the remnant of the fused spinous processes

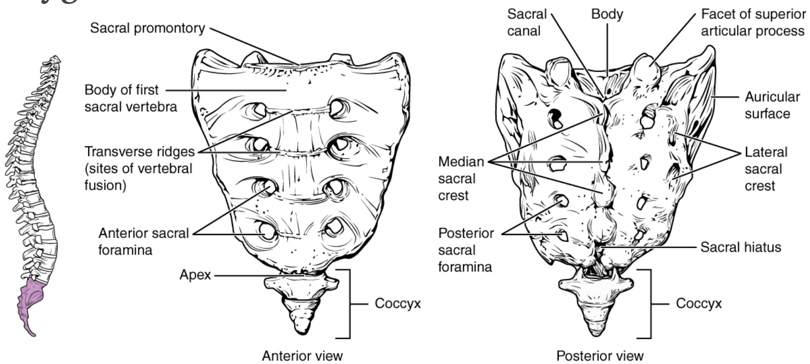
(median = “midline”; while medial = “toward, but not necessarily at, the midline”). Similarly, the fused transverse processes of the sacral vertebrae form the **lateral sacral crest**.

The **sacral promontory** is the anterior lip of the superior base of the sacrum. Lateral to this is the roughened auricular surface, which joins with the ilium portion of the hipbone to form the immobile sacroiliac joints of the pelvis. Passing inferiorly through the sacrum is a bony tunnel called the **sacral canal**, which terminates at the **sacral hiatus** near the inferior tip of the sacrum. The anterior and posterior surfaces of the sacrum have a series of paired openings called **sacral foramina** (singular = foramen) that connect to the sacral canal. Each of these openings is called a **posterior (dorsal) sacral foramen** or **anterior (ventral) sacral foramen**. These openings allow for the anterior and posterior branches of the sacral spinal nerves to exit the sacrum. The **superior articular process of the sacrum**, one of which is found on either side of the superior opening of the sacral canal, articulates with the inferior articular processes from the L5 vertebra.

The coccyx, or tailbone, is derived from the fusion of four very small coccygeal vertebrae (see [link]). It articulates with the inferior tip of the sacrum. It is not weight bearing in the standing position, but may receive some body weight when sitting.

Sacrum and Coccyx

The sacrum is formed from the fusion of five sacral vertebrae, whose lines of fusion are indicated by the transverse ridges. The fused spinous processes form the median sacral crest, while the lateral sacral crest arises from the fused transverse processes. The coccyx is formed by the fusion of four small coccygeal vertebrae.



Intervertebral Discs and Ligaments of the Vertebral Column

The bodies of adjacent vertebrae are strongly anchored to each other by an intervertebral disc. This structure provides padding between the bones during weight bearing, and because it can change shape, also allows for movement between the vertebrae. Although the total amount of movement available between any two adjacent vertebrae is small, when these movements are summed together along the entire length of the vertebral column, large body movements can be produced. Ligaments that extend along the length of the vertebral column

also contribute to its overall support and stability.

Intervertebral Disc

An **intervertebral disc** is a fibrocartilaginous pad that fills the gap between adjacent vertebral bodies (see [link]). Each disc is anchored to the bodies of its adjacent vertebrae, thus strongly uniting these. The discs also provide padding between vertebrae during weight bearing. Because of this, intervertebral discs are thin in the cervical region and thickest in the lumbar region, which carries the most body weight. In total, the intervertebral discs account for approximately 25 percent of your body height between the top of the pelvis and the base of the skull. Intervertebral discs are also flexible and can change shape to allow for movements of the vertebral column.

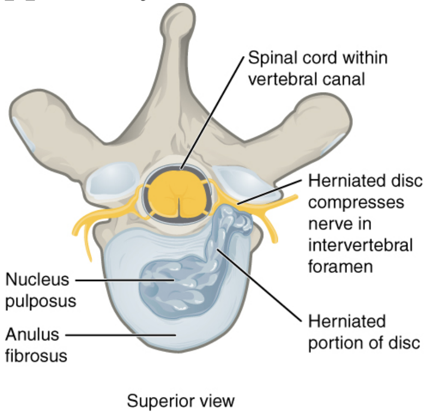
Each intervertebral disc consists of two parts. The **anulus fibrosus** is the tough, fibrous outer layer of the disc. It forms a circle (anulus = "ring" or "circle") and is firmly anchored to the outer margins of the adjacent vertebral bodies. Inside is the **nucleus pulposus**, consisting of a softer, more gel-like material. It has a high water content that serves to resist compression and thus is important for weight bearing. With increasing age, the water content of the nucleus pulposus gradually declines. This causes the disc to become thinner, decreasing total body height somewhat, and reduces the

flexibility and range of motion of the disc, making bending more difficult.

The gel-like nature of the nucleus pulposus also allows the intervertebral disc to change shape as one vertebra rocks side to side or forward and back in relation to its neighbors during movements of the vertebral column. Thus, bending forward causes compression of the anterior portion of the disc but expansion of the posterior disc. If the posterior anulus fibrosus is weakened due to injury or increasing age, the pressure exerted on the disc when bending forward and lifting a heavy object can cause the nucleus pulposus to protrude posteriorly through the anulus fibrosus, resulting in a herniated disc ("ruptured" or "slipped" disc) ([link]). The posterior bulging of the nucleus pulposus can cause compression of a spinal nerve at the point where it exits through the intervertebral foramen, with resulting pain and/or muscle weakness in those body regions supplied by that nerve. The most common sites for disc herniation are the L4/L5 or L5/S1 intervertebral discs, which can cause sciatica, a widespread pain that radiates from the lower back down the thigh and into the leg. Similar injuries of the C5/C6 or C6/C7 intervertebral discs, following forcible hyperflexion of the neck from a collision accident or football injury, can produce pain in the neck, shoulder, and upper limb.

Herniated Intervertebral Disc

Weakening of the anulus fibrosus can result in herniation (protrusion) of the nucleus pulposus and compression of a spinal nerve, resulting in pain and/or muscle weakness in the body regions supplied by that nerve.



Watch this animation to see what it means to “slip” a disk. Watch this second animation to see one possible treatment for a herniated disc, removing and replacing the damaged disc with an artificial one that allows for movement between the adjacent certebrae. How could lifting a heavy

object produce pain in a lower limb?

Ligaments of the Vertebral Column

Adjacent vertebrae are united by ligaments that run the length of the vertebral column along both its posterior and anterior aspects ([link]). These serve to resist excess forward or backward bending movements of the vertebral column, respectively.

The **anterior longitudinal ligament** runs down the anterior side of the entire vertebral column, uniting the vertebral bodies. It serves to resist excess backward bending of the vertebral column. Protection against this movement is particularly important in the neck, where extreme posterior bending of the head and neck can stretch or tear this ligament, resulting in a painful whiplash injury. Prior to the mandatory installation of seat headrests, whiplash injuries were common for passengers involved in a rear-end automobile collision.

The **supraspinous ligament** is located on the posterior side of the vertebral column, where it interconnects the spinous processes of the thoracic and lumbar vertebrae. This strong ligament supports the vertebral column during forward bending motions. In the posterior neck, where the cervical spinous processes are short, the supraspinous

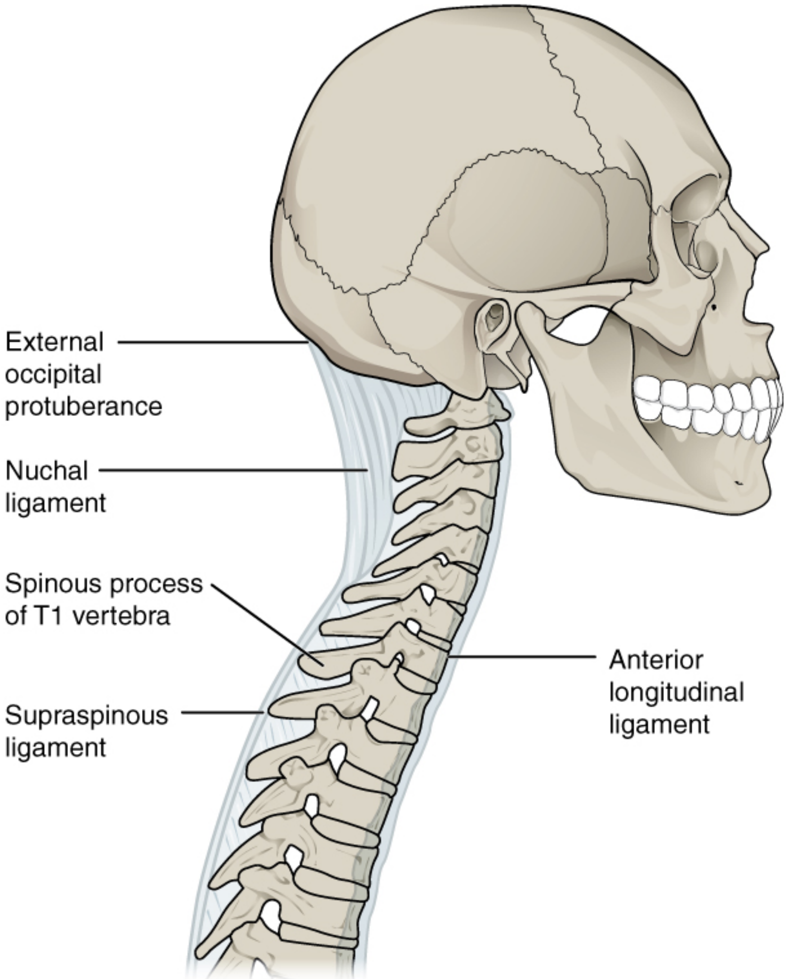
ligament expands to become the **nuchal ligament** (nuchae = "nape" or "back of the neck"). The nuchal ligament is attached to the cervical spinous processes and extends upward and posteriorly to attach to the midline base of the skull, out to the external occipital protuberance. It supports the skull and prevents it from falling forward. This ligament is much larger and stronger in four-legged animals such as cows, where the large skull hangs off the front end of the vertebral column. You can easily feel this ligament by first extending your head backward and pressing down on the posterior midline of your neck. Then tilt your head forward and you will fill the nuchal ligament popping out as it tightens to limit anterior bending of the head and neck.

Additional ligaments are located inside the vertebral canal, next to the spinal cord, along the length of the vertebral column. The **posterior longitudinal ligament** is found anterior to the spinal cord, where it is attached to the posterior sides of the vertebral bodies. Posterior to the spinal cord is the **ligamentum flavum** ("yellow ligament"). This consists of a series of short, paired ligaments, each of which interconnects the lamina regions of adjacent vertebrae. The ligamentum flavum has large numbers of elastic fibers, which have a yellowish color, allowing it to stretch and then pull back. Both of these ligaments provide important support for the vertebral column when bending

forward.

Ligaments of Vertebral Column

The anterior longitudinal ligament runs the length of the vertebral column, uniting the anterior sides of the vertebral bodies. The supraspinous ligament connects the spinous processes of the thoracic and lumbar vertebrae. In the posterior neck, the supraspinous ligament enlarges to form the nuchal ligament, which attaches to the cervical spinous processes and to the base of the skull.


External occipital protuberance
Nuchal ligament
Spinous process of T1 vertebra
Supraspinous ligament
Anterior longitudinal ligament

Use this tool to identify the bones, intervertebral discs, and ligaments of the vertebral column. The thickest portions of the anterior longitudinal ligament and the supraspinous ligament are found in which regions of the vertebral column?

Career Connections

Chiropractor

Chiropractors are health professionals who use nonsurgical techniques to help patients with musculoskeletal system problems that involve the bones, muscles, ligaments, tendons, or nervous system. They treat problems such as neck pain, back pain, joint pain, or headaches. Chiropractors focus on the patient's overall health and can also provide counseling related to lifestyle issues, such as diet, exercise, or sleep problems. If needed, they will refer the patient to other medical specialists. Chiropractors use a drug-free, hands-on approach for patient diagnosis and treatment. They will perform a physical exam, assess the patient's posture and spine, and may perform additional diagnostic tests, including taking X-ray images.

They primarily use manual techniques, such as spinal manipulation, to adjust the patient's spine or other joints. They can recommend therapeutic or rehabilitative exercises, and some also include acupuncture, massage therapy, or ultrasound as part of the treatment program. In addition to those in general practice, some chiropractors specialize in sport injuries, neurology, orthopaedics, pediatrics, nutrition, internal disorders, or diagnostic imaging.

To become a chiropractor, students must have 3–4 years of undergraduate education, attend an accredited, four-year Doctor of Chiropractic (D.C.) degree program, and pass a licensure examination to be licensed for practice in their state. With the aging of the baby-boom generation, employment for chiropractors is expected to increase.

Chapter Review

The vertebral column forms the neck and back. The vertebral column originally develops as 33 vertebrae, but is eventually reduced to 24 vertebrae, plus the sacrum and coccyx. The vertebrae are divided into the cervical region (C1–C7 vertebrae), the thoracic region (T1–T12 vertebrae), and the lumbar region (L1–L5 vertebrae). The sacrum arises

from the fusion of five sacral vertebrae and the coccyx from the fusion of four small coccygeal vertebrae. The vertebral column has four curvatures, the cervical, thoracic, lumbar, and sacrococcygeal curves. The thoracic and sacrococcygeal curves are primary curves retained from the original fetal curvature. The cervical and lumbar curves develop after birth and thus are secondary curves. The cervical curve develops as the infant begins to hold up the head, and the lumbar curve appears with standing and walking.

A typical vertebra consists of an enlarged anterior portion called the body, which provides weight-bearing support. Attached posteriorly to the body is a vertebral arch, which surrounds and defines the vertebral foramen for passage of the spinal cord. The vertebral arch consists of the pedicles, which attach to the vertebral body, and the laminae, which come together to form the roof of the arch. Arising from the vertebral arch are the laterally projecting transverse processes and the posteriorly oriented spinous process. The superior articular processes project upward, where they articulate with the downward projecting inferior articular processes of the next higher vertebrae.

A typical cervical vertebra has a small body, a bifid (Y-shaped) spinous process, and U-shaped transverse processes with a transverse foramen. In addition to these characteristics, the axis (C2 vertebra) also has

the dens projecting upward from the vertebral body. The atlas (C1 vertebra) differs from the other cervical vertebrae in that it does not have a body, but instead consists of bony ring formed by the anterior and posterior arches. The atlas articulates with the dens from the axis. A typical thoracic vertebra is distinguished by its long, downward projecting spinous process. Thoracic vertebrae also have articulation facets on the body and transverse processes for attachment of the ribs. Lumbar vertebrae support the greatest amount of body weight and thus have a large, thick body. They also have a short, blunt spinous process. The sacrum is triangular in shape. The median sacral crest is formed by the fused vertebral spinous processes and the lateral sacral crest is derived from the fused transverse processes. Anterior (ventral) and posterior (dorsal) sacral foramina allow branches of the sacral spinal nerves to exit the sacrum. The auricular surfaces are articulation sites on the lateral sacrum that anchor the sacrum to the hipbones to form the pelvis. The coccyx is small and derived from the fusion of four small vertebrae.

The intervertebral discs fill in the gaps between the bodies of adjacent vertebrae. They provide strong attachments and padding between the vertebrae. The outer, fibrous layer of a disc is called the anulus fibrosus. The gel-like interior is called the nucleus pulposus. The disc can change shape to allow for movement between vertebrae. If the anulus fibrosus

is weakened or damaged, the nucleus pulposus can protrude outward, resulting in a herniated disc.

The anterior longitudinal ligament runs along the full length of the anterior vertebral column, uniting the vertebral bodies. The supraspinous ligament is located posteriorly and interconnects the spinous processes of the thoracic and lumbar vertebrae. In the neck, this ligament expands to become the nuchal ligament. The nuchal ligament is attached to the cervical spinous processes and superiorly to the base of the skull, out to the external occipital protuberance. The posterior longitudinal ligament runs within the vertebral canal and unites the posterior sides of the vertebral bodies. The ligamentum flavum unites the lamina of adjacent vertebrae.

Interactive Link Questions

Osteoporosis is a common age-related bone disease in which bone density and strength is decreased. Watch this video to get a better understanding of how thoracic vertebrae may become weakened and may fractured due to this disease. How may vertebral osteoporosis contribute to kyphosis?

Osteoporosis causes thinning and weakening of the vertebral bodies. When this occurs in thoracic vertebrae, the bodies may collapse producing kyphosis, an enhanced anterior curvature of the thoracic vertebral column.

Watch this animation to see what it means to "slip" a disk. Watch this second animation to see one possible treatment for a herniated disc, removing and replacing the damaged disc with an artificial one that allows for movement between the adjacent certebrae. How could lifting a heavy object produce pain in a lower limb?

Lifting a heavy object can cause an intervertebral disc in the lower back to bulge and compress a spinal nerve as it exits through the intervertebral foramen, thus producing pain in those regions of the lower limb supplied by that nerve.

Use this tool to identify the bones, intervertebral discs, and ligaments of the vertebral column. The thickest portions of the anterior longitudinal ligament and the supraspinous ligament are found in which regions of the vertebral column?

The anterior longitudinal ligament is thickest in the thoracic region of the vertebral column, while the supraspinous ligament is thickest in the lumbar region.

Review Questions

The cervical region of the vertebral column consists of _____.

1. seven vertebrae
2. 12 vertebrae
3. five vertebrae
4. a single bone derived from the fusion of five vertebrae

A

The primary curvatures of the vertebral column _____.

1. include the lumbar curve
2. are remnants of the original fetal curvature
3. include the cervical curve
4. develop after the time of birth

B

A typical vertebra has _____.

1. a vertebral foramen that passes through the body
2. a superior articular process that projects downward to articulate with the superior portion of the next lower vertebra
3. lamina that spans between the transverse process and spinous process
4. a pair of laterally projecting spinous processes

C

A typical lumbar vertebra has _____.

1. a short, rounded spinous process
2. a bifid spinous process
3. articulation sites for ribs
4. a transverse foramen

A

Which is found only in the cervical region of the vertebral column?

1. nuchal ligament
2. ligamentum flavum
3. supraspinous ligament
4. anterior longitudinal ligament

A

Critical Thinking Questions

Describe the vertebral column and define each region.

Answer: The adult vertebral column consists of 24 vertebrae, plus the sacrum and coccyx. The vertebrae are subdivided into cervical, thoracic, and lumbar regions. There are seven cervical vertebrae (C1–C7), 12 thoracic vertebrae (T1–T12), and five lumbar vertebrae (L1–L5). The sacrum is derived from the fusion of five sacral vertebrae and the coccyx is formed by the fusion of four small coccygeal vertebrae.

Describe a typical vertebra.

A typical vertebra consists of an anterior body

and a posterior vertebral arch. The body serves for weight bearing. The vertebral arch surrounds and protects the spinal cord. The vertebral arch is formed by the pedicles, which are attached to the posterior side of the vertebral body, and the lamina, which come together to form the top of the arch. A pair of transverse processes extends laterally from the vertebral arch, at the junction between each pedicle and lamina. The spinous process extends posteriorly from the top of the arch. A pair of superior articular processes project upward and a pair of inferior articular processes project downward. Together, the notches found in the margins of the pedicles of adjacent vertebrae form an intervertebral foramen.

Describe the sacrum.

The sacrum is a single, triangular-shaped bone formed by the fusion of five sacral vertebrae. On the posterior sacrum, the median sacral crest is derived from the fused spinous processes, and the lateral sacral crest results from the fused transverse processes. The sacral canal contains the sacral spinal nerves, which exit via the anterior (ventral) and posterior (dorsal) sacral foramina. The sacral promontory is the anterior lip. The sacrum also forms the

posterior portion of the pelvis.

Describe the structure and function of an intervertebral disc.

An intervertebral disc fills in the space between adjacent vertebrae, where it provides padding and weight-bearing ability, and allows for movements between the vertebrae. It consists of an outer anulus fibrosus and an inner nucleus pulposus. The anulus fibrosus strongly anchors the adjacent vertebrae to each other, and the high water content of the nucleus pulposus resists compression for weight bearing and can change shape to allow for vertebral column movements.

Define the ligaments of the vertebral column.

The anterior longitudinal ligament is attached to the vertebral bodies on the anterior side of the vertebral column. The supraspinous ligament is located on the posterior side, where it interconnects the thoracic and lumbar spinous processes. In the posterior neck, this ligament expands to become the nuchal ligament, which attaches to the cervical spinous processes and the base of the skull. The

posterior longitudinal ligament and ligamentum flavum are located inside the vertebral canal. The posterior longitudinal ligament unites the posterior sides of the vertebral bodies. The ligamentum flavum unites the lamina of adjacent vertebrae.

Glossary

anterior arch
: anterior portion of the ring-like C1 (atlas) vertebra

anterior longitudinal ligament
: ligament that runs the length of the vertebral column, uniting the anterior aspects of the vertebral bodies

anterior (ventral) sacral foramen
: one of the series of paired openings located on the anterior (ventral) side of the sacrum

anulus fibrosus
: tough, fibrous outer portion of an intervertebral disc, which is strongly anchored to the bodies of the adjacent vertebrae

atlas
: first cervical (C1) vertebra

axis
: second cervical (C2) vertebra

cervical curve
: posteriorly concave curvature of the cervical vertebral column region; a secondary curve of the vertebral column

cervical vertebrae
: seven vertebrae numbered as C1–C7 that are located in the neck region of the vertebral column

costal facet
: site on the lateral sides of a thoracic vertebra for articulation with the head of a rib

dens
: bony projection (odontoid process) that extends upward from the body of the C2 (axis) vertebra

facet
: small, flattened area on a bone for an articulation (joint) with another bone, or for muscle attachment

inferior articular process
: bony process that extends downward from the vertebral arch of a vertebra that articulates with the superior articular process of the next lower vertebra

intervertebral disc
: structure located between the bodies of adjacent vertebrae that strongly joins the vertebrae; provides padding, weight bearing ability, and enables vertebral column movements

intervertebral foramen
: opening located between adjacent vertebrae for exit of a spinal nerve

kyphosis
: (also, humpback or hunchback) excessive posterior curvature of the thoracic vertebral column region

lamina
: portion of the vertebral arch on each vertebra that extends between the transverse and spinous process

lateral sacral crest
: paired irregular ridges running down the lateral sides of the posterior sacrum that was formed by the fusion of the transverse processes from the five sacral vertebrae

ligamentum flavum
: series of short ligaments that unite the lamina of adjacent vertebrae

lordosis

(also, swayback) excessive anterior curvature of the lumbar vertebral column region

lumbar curve
: posteriorly concave curvature of the lumbar vertebral column region; a secondary curve of the vertebral column

lumbar vertebrae
: five vertebrae numbered as L1–L5 that are located in lumbar region (lower back) of the vertebral column

median sacral crest
: irregular ridge running down the midline of the posterior sacrum that was formed from the fusion of the spinous processes of the five sacral vertebrae

nuchal ligament
: expanded portion of the supraspinous ligament within the posterior neck; interconnects the spinous processes of the cervical vertebrae and attaches to the base of the skull

nucleus pulposus
: gel-like central region of an intervertebral disc; provides for padding, weight-bearing, and movement between adjacent vertebrae

pedicle

portion of the vertebral arch that extends from the vertebral body to the transverse process

posterior arch
: posterior portion of the ring-like C1 (atlas) vertebra

posterior longitudinal ligament
: ligament that runs the length of the vertebral column, uniting the posterior sides of the vertebral bodies

posterior (dorsal) sacral foramen
: one of the series of paired openings located on the posterior (dorsal) side of the sacrum

primary curve
: anteriorly concave curvatures of the thoracic and sacrococcygeal regions that are retained from the original fetal curvature of the vertebral column

sacral canal
: bony tunnel that runs through the sacrum

sacral foramina
: series of paired openings for nerve exit located on both the anterior (ventral) and posterior (dorsal) aspects of the sacrum

sacral hiatus

inferior opening and termination of the sacral canal

sacral promontory
: anterior lip of the base (superior end) of the sacrum

sacrococcygeal curve
: anteriorly concave curvature formed by the sacrum and coccyx; a primary curve of the vertebral column

scoliosis
: abnormal lateral curvature of the vertebral column

secondary curve
: posteriorly concave curvatures of the cervical and lumbar regions of the vertebral column that develop after the time of birth

spinous process
: unpaired bony process that extends posteriorly from the vertebral arch of a vertebra

superior articular process
: bony process that extends upward from the vertebral arch of a vertebra that articulates with the inferior articular process of the next higher vertebra

superior articular process of the sacrum
: paired processes that extend upward from the sacrum to articulate (join) with the inferior articular processes from the L5 vertebra

supraspinous ligament
: ligament that interconnects the spinous processes of the thoracic and lumbar vertebrae

thoracic curve
: anteriorly concave curvature of the thoracic vertebral column region; a primary curve of the vertebral column

thoracic vertebrae
: twelve vertebrae numbered as T1–T12 that are located in the thoracic region (upper back) of the vertebral column

transverse foramen
: opening found only in the transverse processes of cervical vertebrae

transverse process
: paired bony processes that extends laterally from the vertebral arch of a vertebra

vertebral arch
: bony arch formed by the posterior portion of each vertebra that surrounds and protects the spinal cord

vertebral (spinal) canal
: bony passageway within the vertebral column for the spinal cord that is formed by the series of individual vertebral foramina

vertebral foramen
: opening associated with each vertebra defined by the vertebral arch that provides passage for the spinal cord

The Thoracic Cage

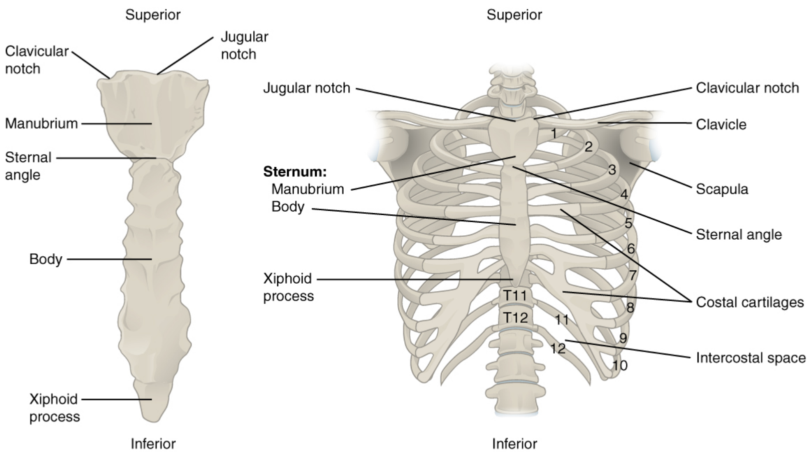
By the end of this section, you will be able to:

- Discuss the components that make up the thoracic cage
- Identify the parts of the sternum and define the sternal angle
- Discuss the parts of a rib and rib classifications

The thoracic cage (rib cage) forms the thorax (chest) portion of the body. It consists of the 12 pairs of ribs with their costal cartilages and the sternum ([link]). The ribs are anchored posteriorly to the 12 thoracic vertebrae (T1–T12). The thoracic cage protects the heart and lungs.

Thoracic Cage

The thoracic cage is formed by the (a) sternum and (b) 12 pairs of ribs with their costal cartilages. The ribs are anchored posteriorly to the 12 thoracic vertebrae. The sternum consists of the manubrium, body, and xiphoid process. The ribs are classified as true ribs (1–7) and false ribs (8–12). The last two pairs of false ribs are also known as floating ribs (11–12).



(a) Anterior view of sternum (b) Anterior view of skeleton of thorax

Sternum

The sternum is the elongated bony structure that anchors the anterior thoracic cage. It consists of three parts: the manubrium, body, and xiphoid process. The **manubrium** is the wider, superior portion of the sternum. The top of the manubrium has a shallow, U-shaped border called the **jugular (suprasternal) notch**. This can be easily felt at the anterior base of the neck, between the medial ends of the clavicles. The **clavicular notch** is the shallow depression located on either side at the superior-lateral margins of the manubrium. This is the site of the sternoclavicular joint, between the sternum and clavicle. The first ribs also attach to the manubrium.

The elongated, central portion of the sternum is the body. The manubrium and body join together at the

sternal angle, so called because the junction between these two components is not flat, but forms a slight bend. The second rib attaches to the sternum at the sternal angle. Since the first rib is hidden behind the clavicle, the second rib is the highest rib that can be identified by palpation. Thus, the sternal angle and second rib are important landmarks for the identification and counting of the lower ribs. Ribs 3–7 attach to the sternal body.

The inferior tip of the sternum is the **xiphoid process**. This small structure is cartilaginous early in life, but gradually becomes ossified starting during middle age.

Ribs

Each rib is a curved, flattened bone that contributes to the wall of the thorax. The ribs articulate posteriorly with the T1–T12 thoracic vertebrae, and most attach anteriorly via their costal cartilages to the sternum. There are 12 pairs of ribs. The ribs are numbered 1–12 in accordance with the thoracic vertebrae.

Parts of a Typical Rib

The posterior end of a typical rib is called the **head of the rib** (see [link]). This region articulates

primarily with the costal facet located on the body of the same numbered thoracic vertebra and to a lesser degree, with the costal facet located on the body of the next higher vertebra. Lateral to the head is the narrowed **neck of the rib**. A small bump on the posterior rib surface is the **tubercle of the rib**, which articulates with the facet located on the transverse process of the same numbered vertebra. The remainder of the rib is the **body of the rib** (shaft). Just lateral to the tubercle is the **angle of the rib**, the point at which the rib has its greatest degree of curvature. The angles of the ribs form the most posterior extent of the thoracic cage. In the anatomical position, the angles align with the medial border of the scapula. A shallow **costal groove** for the passage of blood vessels and a nerve is found along the inferior margin of each rib.

Rib Classifications

The bony ribs do not extend anteriorly completely around to the sternum. Instead, each rib ends in a **costal cartilage**. These cartilages are made of hyaline cartilage and can extend for several inches. Most ribs are then attached, either directly or indirectly, to the sternum via their costal cartilage (see [link]). The ribs are classified into three groups based on their relationship to the sternum.

Ribs 1–7 are classified as **true ribs** (vertebrosternal ribs). The costal cartilage from each of these ribs

attaches directly to the sternum. Ribs 8–12 are called **false ribs** (vertebrochondral ribs). The costal cartilages from these ribs do not attach directly to the sternum. For ribs 8–10, the costal cartilages are attached to the cartilage of the next higher rib. Thus, the cartilage of rib 10 attaches to the cartilage of rib 9, rib 9 then attaches to rib 8, and rib 8 is attached to rib 7. The last two false ribs (11–12) are also called **floating ribs** (vertebral ribs). These are short ribs that do not attach to the sternum at all. Instead, their small costal cartilages terminate within the musculature of the lateral abdominal wall.

Chapter Review

The thoracic cage protects the heart and lungs. It is composed of 12 pairs of ribs with their costal cartilages and the sternum. The ribs are anchored posteriorly to the 12 thoracic vertebrae. The sternum consists of the manubrium, body, and xiphoid process. The manubrium and body are joined at the sternal angle, which is also the site for attachment of the second ribs.

Ribs are flattened, curved bones and are numbered 1–12. Posteriorly, the head of the rib articulates with the costal facets located on the bodies of thoracic vertebrae and the rib tubercle articulates with the facet located on the vertebral transverse

process. The angle of the ribs forms the most posterior portion of the thoracic cage. The costal groove in the inferior margin of each rib carries blood vessels and a nerve. Anteriorly, each rib ends in a costal cartilage. True ribs (1–7) attach directly to the sternum via their costal cartilage. The false ribs (8–12) either attach to the sternum indirectly or not at all. Ribs 8–10 have their costal cartilages attached to the cartilage of the next higher rib. The floating ribs (11–12) are short and do not attach to the sternum or to another rib.

Review Questions

The sternum _____.

1. consists of only two parts, the manubrium and xiphoid process
2. has the sternal angle located between the manubrium and body
3. receives direct attachments from the costal cartilages of all 12 pairs of ribs
4. articulates directly with the thoracic vertebrae

B

The sternal angle is the _____.

1. junction between the body and xiphoid process
2. site for attachment of the clavicle
3. site for attachment of the floating ribs
4. junction between the manubrium and body

D

The tubercle of a rib _____.

1. is for articulation with the transverse process of a thoracic vertebra
2. is for articulation with the body of a thoracic vertebra
3. provides for passage of blood vessels and a nerve
4. is the area of greatest rib curvature

A

True ribs are _____.

1. ribs 8–12
2. attached via their costal cartilage to the next higher rib
3. made entirely of bone, and thus do not

have a costal cartilage
4. attached via their costal cartilage directly to the sternum

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D

Critical Thinking Questions

Define the parts and functions of the thoracic cage.

The thoracic cage is formed by the 12 pairs of ribs with their costal cartilages and the sternum. The ribs are attached posteriorly to the 12 thoracic vertebrae and most are anchored anteriorly either directly or indirectly to the sternum. The thoracic cage functions to protect the heart and lungs.

Describe the parts of the sternum.

The sternum consists of the manubrium, body, and xiphoid process. The manubrium forms the expanded, superior end of the sternum. It has a jugular (suprasternal) notch, a pair of clavicular

notches for articulation with the clavicles, and receives the costal cartilage of the first rib. The manubrium is joined to the body of the sternum at the sternal angle, which is also the site for attachment of the second rib costal cartilages. The body receives the costal cartilage attachments for ribs 3–7. The small xiphoid process forms the inferior tip of the sternum.

Discuss the parts of a typical rib.

A typical rib is a flattened, curved bone. The head of a rib is attached posteriorly to the costal facets of the thoracic vertebrae. The rib tubercle articulates with the transverse process of a thoracic vertebra. The angle is the area of greatest rib curvature and forms the largest portion of the thoracic cage. The body (shaft) of a rib extends anteriorly and terminates at the attachment to its costal cartilage. The shallow costal groove runs along the inferior margin of a rib and carries blood vessels and a nerve.

Define the classes of ribs.

Ribs are classified based on if and how their costal cartilages attach to the sternum. True (vertebrosternal) ribs are ribs 1–7. The costal

cartilage for each of these attaches directly to the sternum. False (vertebrochondral) ribs, 8–12, are attached either indirectly or not at all to the sternum. Ribs 8–10 are attached indirectly to the sternum. For these ribs, the costal cartilage of each attaches to the cartilage of the next higher rib. The last false ribs (11–12) are also called floating (vertebral) ribs, because these ribs do not attach to the sternum at all. Instead, the ribs and their small costal cartilages terminate within the muscles of the lateral abdominal wall.

Glossary

angle of the rib
: portion of rib with greatest curvature; together, the rib angles form the most posterior extent of the thoracic cage

body of the rib
: shaft portion of a rib

clavicular notch
: paired notches located on the superior-lateral sides of the sternal manubrium, for articulation with the clavicle

costal cartilage
: hyaline cartilage structure attached to the anterior end of each rib that provides for

either direct or indirect attachment of most ribs to the sternum

costal groove
: shallow groove along the inferior margin of a rib that provides passage for blood vessels and a nerve

false ribs
: vertebrochondral ribs 8–12 whose costal cartilage either attaches indirectly to the sternum via the costal cartilage of the next higher rib or does not attach to the sternum at all

floating ribs
: vertebral ribs 11–12 that do not attach to the sternum or to the costal cartilage of another rib

head of the rib
: posterior end of a rib that articulates with the bodies of thoracic vertebrae

jugular (suprasternal) notch
: shallow notch located on superior surface of sternal manubrium

manubrium
: expanded, superior portion of the sternum

neck of the rib

narrowed region of a rib, next to the rib head

sterna angle

junction line between manubrium and body of the sternum and the site for attachment of the second rib to the sternum

true ribs

vertebrosternal ribs 1–7 that attach via their costal cartilage directly to the sternum

tubercle of the rib

small bump on the posterior side of a rib for articulation with the transverse process of a thoracic vertebra

xiphoid process

small process that forms the inferior tip of the sternum

Embryonic Development of the Axial Skeleton
By the end of this section, you will be able to:

- Discuss the two types of embryonic bone development within the skull
- Describe the development of the vertebral column and thoracic cage

The axial skeleton begins to form during early embryonic development. However, growth, remodeling, and ossification (bone formation) continue for several decades after birth before the adult skeleton is fully formed. Knowledge of the developmental processes that give rise to the skeleton is important for understanding the abnormalities that may arise in skeletal structures.

Development of the Skull

During the third week of embryonic development, a rod-like structure called the **notochord** develops dorsally along the length of the embryo. The tissue overlying the notochord enlarges and forms the neural tube, which will give rise to the brain and spinal cord. By the fourth week, mesoderm tissue located on either side of the notochord thickens and separates into a repeating series of block-like tissue structures, each of which is called a **somite**. As the somites enlarge, each one will split into several

parts. The most medial of these parts is called a **sclerotome**. The sclerotomes consist of an embryonic tissue called mesenchyme, which will give rise to the fibrous connective tissues, cartilages, and bones of the body.

The bones of the skull arise from mesenchyme during embryonic development in two different ways. The first mechanism produces the bones that form the top and sides of the brain case. This involves the local accumulation of mesenchymal cells at the site of the future bone. These cells then differentiate directly into bone producing cells, which form the skull bones through the process of intramembranous ossification. As the brain case bones grow in the fetal skull, they remain separated from each other by large areas of dense connective tissue, each of which is called a **fontanelle** ([link]). The fontanelles are the soft spots on an infant's head. They are important during birth because these areas allow the skull to change shape as it squeezes through the birth canal. After birth, the fontanelles allow for continued growth and expansion of the skull as the brain enlarges. The largest fontanelle is located on the anterior head, at the junction of the frontal and parietal bones. The fontanelles decrease in size and disappear by age 2. However, the skull bones remained separated from each other at the sutures, which contain dense fibrous connective tissue that unites the adjacent bones. The connective tissue of the sutures allows for continued growth of

the skull bones as the brain enlarges during childhood growth.

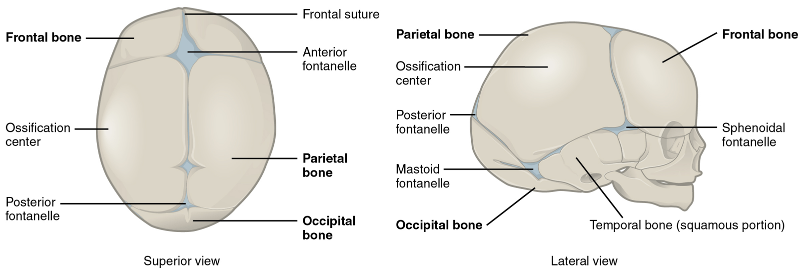
The second mechanism for bone development in the skull produces the facial bones and floor of the brain case. This also begins with the localized accumulation of mesenchymal cells. However, these cells differentiate into cartilage cells, which produce a hyaline cartilage model of the future bone. As this cartilage model grows, it is gradually converted into bone through the process of endochondral ossification. This is a slow process and the cartilage is not completely converted to bone until the skull achieves its full adult size.

At birth, the brain case and orbits of the skull are disproportionally large compared to the bones of the jaws and lower face. This reflects the relative underdevelopment of the maxilla and mandible, which lack teeth, and the small sizes of the paranasal sinuses and nasal cavity. During early childhood, the mastoid process enlarges, the two halves of the mandible and frontal bone fuse together to form single bones, and the paranasal sinuses enlarge. The jaws also expand as the teeth begin to appear. These changes all contribute to the rapid growth and enlargement of the face during childhood.

Newborn Skull

The bones of the newborn skull are not fully ossified and are separated by large areas called fontanelles,

which are filled with fibrous connective tissue. The fontanelles allow for continued growth of the skull after birth. At the time of birth, the facial bones are small and underdeveloped, and the mastoid process has not yet formed.



Development of the Vertebral Column and Thoracic cage

Development of the vertebrae begins with the accumulation of mesenchyme cells from each sclerotome around the notochord. These cells differentiate into a hyaline cartilage model for each vertebra, which then grow and eventually ossify into bone through the process of endochondral ossification. As the developing vertebrae grow, the notochord largely disappears. However, small areas of notochord tissue persist between the adjacent vertebrae and this contributes to the formation of each intervertebral disc.

The ribs and sternum also develop from mesenchyme. The ribs initially develop as part of the cartilage model for each vertebra, but in the

thorax region, the rib portion separates from the vertebra by the eighth week. The cartilage model of the rib then ossifies, except for the anterior portion, which remains as the costal cartilage. The sternum initially forms as paired hyaline cartilage models on either side of the anterior midline, beginning during the fifth week of development. The cartilage models of the ribs become attached to the lateral sides of the developing sternum. Eventually, the two halves of the cartilaginous sternum fuse together along the midline and then ossify into bone. The manubrium and body of the sternum are converted into bone first, with the xiphoid process remaining as cartilage until late in life.

View this video to review the two processes that give rise to the bones of the skull and body. What are the two mechanisms by which the bones of the body are formed and which bones are formed by each mechanism?

Homeostatic Imbalances

Craniosynostosis

The premature closure (fusion) of a suture line is a condition called craniosynostosis. This error in the normal developmental process results in abnormal growth of the skull and deformity of the head. It is produced either by defects in the ossification process of the skull bones or failure of the brain to properly enlarge. Genetic factors are involved, but the underlying cause is unknown. It is a relatively common condition, occurring in approximately 1:2000 births, with males being more commonly affected. Primary craniosynostosis involves the early fusion of one cranial suture, whereas complex craniosynostosis results from the premature fusion of several sutures.

The early fusion of a suture in primary craniosynostosis prevents any additional enlargement of the cranial bones and skull along this line. Continued growth of the brain and skull is therefore diverted to other areas of the head, causing an abnormal enlargement of these regions. For example, the early disappearance of the anterior fontanelle and premature closure of the sagittal suture prevents growth across the top of the head. This is compensated by upward growth by the bones of the lateral skull, resulting in a long, narrow, wedge-shaped head. This condition, known as scaphocephaly, accounts for approximately 50 percent of craniosynostosis abnormalities.

Although the skull is misshapen, the brain still has

adequate room to grow and thus there is no accompanying abnormal neurological development.

In cases of complex craniosynostosis, several sutures close prematurely. The amount and degree of skull deformity is determined by the location and extent of the sutures involved. This results in more severe constraints on skull growth, which can alter or impede proper brain growth and development.

Cases of craniosynostosis are usually treated with surgery. A team of physicians will open the skull along the fused suture, which will then allow the skull bones to resume their growth in this area. In some cases, parts of the skull will be removed and replaced with an artificial plate. The earlier after birth that surgery is performed, the better the outcome. After treatment, most children continue to grow and develop normally and do not exhibit any neurological problems.

Chapter Review

Formation of the axial skeleton begins during early embryonic development with the appearance of the rod-like notochord along the dorsal length of the early embryo. Repeating, paired blocks of tissue

called somites then appear along either side of notochord. As the somites grow, they split into parts, one of which is called a sclerotome. This consists of mesenchyme, the embryonic tissue that will become the bones, cartilages, and connective tissues of the body.

Mesenchyme in the head region will produce the bones of the skull via two different mechanisms. The bones of the brain case arise via intramembranous ossification in which embryonic mesenchyme tissue converts directly into bone. At the time of birth, these bones are separated by fontanelles, wide areas of fibrous connective tissue. As the bones grow, the fontanelles are reduced to sutures, which allow for continued growth of the skull throughout childhood. In contrast, the cranial base and facial bones are produced by the process of endochondral ossification, in which mesenchyme tissue initially produces a hyaline cartilage model of the future bone. The cartilage model allows for growth of the bone and is gradually converted into bone over a period of many years.

The vertebrae, ribs, and sternum also develop via endochondral ossification. Mesenchyme accumulates around the notochord and produces hyaline cartilage models of the vertebrae. The notochord largely disappears, but remnants of the notochord contribute to formation of the intervertebral discs. In the thorax region, a portion

of the vertebral cartilage model splits off to form the ribs. These then become attached anteriorly to the developing cartilage model of the sternum. Growth of the cartilage models for the vertebrae, ribs, and sternum allow for enlargement of the thoracic cage during childhood and adolescence. The cartilage models gradually undergo ossification and are converted into bone.

Interactive Link Questions

View this video to review the two processes that give rise to the bones of the skull and body. What are the two mechanisms by which the bones of the body are formed and which bones are formed by each mechanism?

Bones on the top and sides of the skull develop when fibrous membrane areas ossify (convert) into bone. The bones of the limbs, ribs, and vertebrae develop when cartilage models of the bones ossify into bone.

Review Questions

Embryonic development of the axial skeleton involves _____.

1. intramembranous ossification, which forms the facial bones.
2. endochondral ossification, which forms the ribs and sternum
3. the notochord, which produces the cartilage models for the vertebrae
4. the formation of hyaline cartilage models, which give rise to the flat bones of the skull

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B

A fontanelle _____.

1. is the cartilage model for a vertebra that later is converted into bone
2. gives rise to the facial bones and vertebrae
3. is the rod-like structure that runs the length of the early embryo
4. is the area of fibrous connective tissue found at birth between the brain case bones

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D

Critical Thinking Questions

Discuss the processes by which the brain-case bones of the skull are formed and grow during skull enlargement.

The brain-case bones that form the top and sides of the skull are produced by intramembranous ossification. In this, mesenchyme from the sclerotome portion of the somites accumulates at the site of the future bone and differentiates into bone-producing cells. These generate areas of bone that are initially separated by wide regions of fibrous connective tissue called fontanelles. After birth, as the bones enlarge, the fontanelles disappear. However, the bones remain separated by the sutures, where bone and skull growth can continue until the adult size is obtained.

Discuss the process that gives rise to the base and facial bones of the skull.

The facial bones and base of the skull arise via the process of endochondral ossification. This process begins with the localized accumulation of mesenchyme tissue at the sites of the future

bones. The mesenchyme differentiates into hyaline cartilage, which forms a cartilage model of the future bone. The cartilage allows for growth and enlargement of the model. It is gradually converted into bone over time.

Discuss the development of the vertebrae, ribs, and sternum.

The vertebrae, ribs, and sternum all develop via the process of endochondral ossification. Mesenchyme tissue from the sclerotome portion of the somites accumulates on either side of the notochord and produces hyaline cartilage models for each vertebra. In the thorax region, a portion of this cartilage model splits off to form the ribs. Similarly, mesenchyme forms cartilage models for the right and left halves of the sternum. The ribs then become attached anteriorly to the developing sternum, and the two halves of sternum fuse together. Ossification of the cartilage model into bone occurs within these structures over time. This process continues until each is converted into bone, except for the sternal ends of the ribs, which remain as the costal cartilages.

Glossary

fontanelle
: expanded area of fibrous connective tissue that separates the brain case bones of the skull prior to birth and during the first year after birth

notochord
: rod-like structure along dorsal side of the early embryo; largely disappears during later development but does contribute to formation of the intervertebral discs

sclerotome
: medial portion of a somite consisting of mesenchyme tissue that will give rise to bone, cartilage, and fibrous connective tissues

somite
: one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

Introduction
class="introduction"
Girl Kayaking
Without joints, body movements would be impossible. (credit: Graham Richardson/flickr.com)


Chapter Objectives

After this chapter, you will be able to:

- Discuss both functional and structural classifications for body joints
- Describe the characteristic features for fibrous, cartilaginous, and synovial joints and give examples of each
- Define and identify the different body

movements
- Discuss the structure of specific body joints and the movements allowed by each
- Explain the development of body joints

The adult human body has 206 bones, and with the exception of the hyoid bone in the neck, each bone is connected to at least one other bone. Joints are the location where bones come together. Many joints allow for movement between the bones. At these joints, the articulating surfaces of the adjacent bones can move smoothly against each other. However, the bones of other joints may be joined to each other by connective tissue or cartilage. These joints are designed for stability and provide for little or no movement. Importantly, joint stability and movement are related to each other. This means that stable joints allow for little or no mobility between the adjacent bones. Conversely, joints that provide the most movement between bones are the least stable. Understanding the relationship between joint structure and function will help to explain why particular types of joints are found in certain areas of the body.

The articulating surfaces of bones at stable types of joints, with little or no mobility, are strongly united to each other. For example, most of the joints of the skull are held together by fibrous connective tissue

and do not allow for movement between the adjacent bones. This lack of mobility is important, because the skull bones serve to protect the brain. Similarly, other joints united by fibrous connective tissue allow for very little movement, which provides stability and weight-bearing support for the body. For example, the tibia and fibula of the leg are tightly united to give stability to the body when standing. At other joints, the bones are held together by cartilage, which permits limited movements between the bones. Thus, the joints of the vertebral column only allow for small movements between adjacent vertebrae, but when added together, these movements provide the flexibility that allows your body to twist, or bend to the front, back, or side. In contrast, at joints that allow for wide ranges of motion, the articulating surfaces of the bones are not directly united to each other. Instead, these surfaces are enclosed within a space filled with lubricating fluid, which allows the bones to move smoothly against each other. These joints provide greater mobility, but since the bones are free to move in relation to each other, the joint is less stable. Most of the joints between the bones of the appendicular skeleton are this freely moveable type of joint. These joints allow the muscles of the body to pull on a bone and thereby produce movement of that body region. Your ability to kick a soccer ball, pick up a fork, and dance the tango depend on mobility at these types of joints.

Classification of Joints

By the end of this section, you will be able to:

- Distinguish between the functional and structural classifications for joints
- Describe the three functional types of joints and give an example of each
- List the three types of diarthrodial joints

A **joint**, also called an **articulation**, is any place where adjacent bones or bone and cartilage come together (articulate with each other) to form a connection. Joints are classified both structurally and functionally. Structural classifications of joints take into account whether the adjacent bones are strongly anchored to each other by fibrous connective tissue or cartilage, or whether the adjacent bones articulate with each other within a fluid-filled space called a **joint cavity**. Functional classifications describe the degree of movement available between the bones, ranging from immobile, to slightly mobile, to freely moveable joints. The amount of movement available at a particular joint of the body is related to the functional requirements for that joint. Thus immobile or slightly moveable joints serve to protect internal organs, give stability to the body, and allow for limited body movement. In contrast, freely moveable joints allow for much more extensive movements of the body and limbs.

Structural Classification of Joints

The structural classification of joints is based on whether the articulating surfaces of the adjacent bones are directly connected by fibrous connective tissue or cartilage, or whether the articulating surfaces contact each other within a fluid-filled joint cavity. These differences serve to divide the joints of the body into three structural classifications. A **fibrous joint** is where the adjacent bones are united by fibrous connective tissue. At a **cartilaginous joint**, the bones are joined by hyaline cartilage or fibrocartilage. At a **synovial joint**, the articulating surfaces of the bones are not directly connected, but instead come into contact with each other within a joint cavity that is filled with a lubricating fluid. Synovial joints allow for free movement between the bones and are the most common joints of the body.

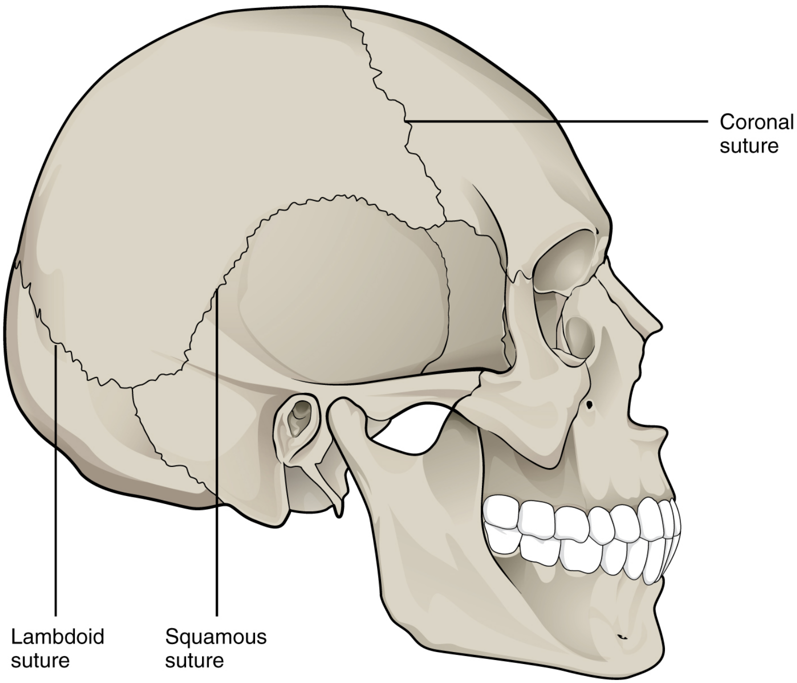
Functional Classification of Joints

The functional classification of joints is determined by the amount of mobility found between the adjacent bones. Joints are thus functionally classified as a synarthrosis or immobile joint, an amphiarthrosis or slightly moveable joint, or as a diarthrosis, which is a freely moveable joint (arthroun = "to fasten by a joint"). Depending on their location, fibrous joints may be functionally

classified as a synarthrosis (immobile joint) or an amphiarthrosis (slightly mobile joint). Cartilaginous joints are also functionally classified as either a synarthrosis or an amphiarthrosis joint. All synovial joints are functionally classified as a diarthrosis joint.

Synarthrosis

An immobile or nearly immobile joint is called a **synarthrosis**. The immobile nature of these joints provide for a strong union between the articulating bones. This is important at locations where the bones provide protection for internal organs. Examples include sutures, the fibrous joints between the bones of the skull that surround and protect the brain ([link]), and the manubriosternal joint, the cartilaginous joint that unites the manubrium and body of the sternum for protection of the heart.
Suture Joints of Skull
The suture joints of the skull are an example of a synarthrosis, an immobile or essentially immobile joint.



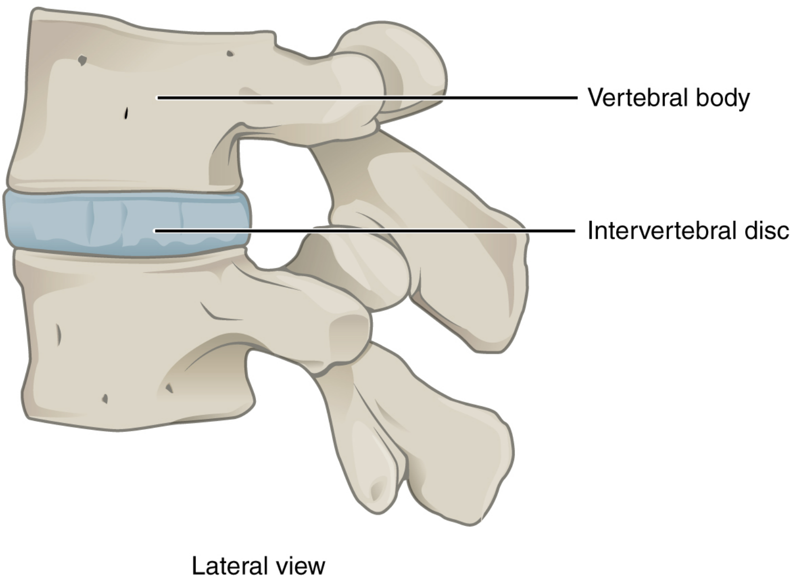
Amphiarthrosis

An **amphiarthrosis** is a joint that has limited mobility. An example of this type of joint is the cartilaginous joint that unites the bodies of adjacent vertebrae. Filling the gap between the vertebrae is a thick pad of fibrocartilage called an intervertebral disc ([link]). Each intervertebral disc strongly unites the vertebrae but still allows for a limited amount of movement between them. However, the small movements available between adjacent vertebrae can sum together along the length of the vertebral column to provide for large ranges of body movements.

Another example of an amphiarthrosis is the pubic symphysis of the pelvis. This is a cartilaginous joint in which the pubic regions of the right and left hip bones are strongly anchored to each other by fibrocartilage. This joint normally has very little mobility. The strength of the pubic symphysis is important in conferring weight-bearing stability to the pelvis.

Intervertebral Disc

An intervertebral disc unites the bodies of adjacent vertebrae within the vertebral column. Each disc allows for limited movement between the vertebrae and thus functionally forms an amphiarthrosis type of joint. Intervertebral discs are made of fibrocartilage and thereby structurally form a symphysis type of cartilaginous joint.



Diarthrosis

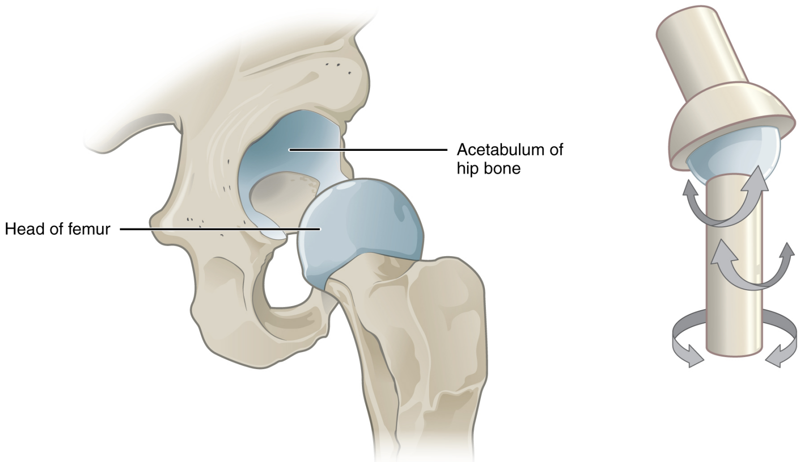
A freely mobile joint is classified as a **diarthrosis**. These types of joints include all synovial joints of the body, which provide the majority of body movements. Most diarthrotic joints are found in the appendicular skeleton and thus give the limbs a wide range of motion. These joints are divided into three categories, based on the number of axes of motion provided by each. An axis in anatomy is described as the movements in reference to the three anatomical planes: transverse, frontal, and sagittal. Thus, diarthroses are classified as uniaxial (for movement in one plane), biaxial (for movement in two planes), or multiaxial joints (for movement in all three anatomical planes).

A **uniaxial joint** only allows for a motion in a single plane (around a single axis). The elbow joint, which only allows for bending or straightening, is an example of a uniaxial joint. A **biaxial joint** allows for motions within two planes. An example of a biaxial joint is a metacarpophalangeal joint (knuckle joint) of the hand. The joint allows for movement along one axis to produce bending or straightening of the finger, and movement along a second axis, which allows for spreading of the fingers away from each other and bringing them together. A joint that allows for the several directions of movement is called a **multiaxial joint** (polyaxial or triaxial joint). This type of diarthrotic joint allows for movement along three axes ([link]). The shoulder and hip joints are multiaxial joints. They allow the

upper or lower limb to move in an anterior-posterior direction and a medial-lateral direction. In addition, the limb can also be rotated around its long axis. This third movement results in rotation of the limb so that its anterior surface is moved either toward or away from the midline of the body.

Multiaxial Joint

A multiaxial joint, such as the hip joint, allows for three types of movement: anterior-posterior, medial-lateral, and rotational.



Chapter Review

Structural classifications of the body joints are based on how the bones are held together and articulate with each other. At fibrous joints, the adjacent bones are directly united to each other by fibrous connective tissue. Similarly, at a cartilaginous joint, the adjacent bones are united by cartilage. In

contrast, at a synovial joint, the articulating bone surfaces are not directly united to each other, but come together within a fluid-filled joint cavity.

The functional classification of body joints is based on the degree of movement found at each joint. A synarthrosis is a joint that is essentially immobile. This type of joint provides for a strong connection between the adjacent bones, which serves to protect internal structures such as the brain or heart. Examples include the fibrous joints of the skull sutures and the cartilaginous manubriosternal joint. A joint that allows for limited movement is an amphiarthrosis. An example is the pubic symphysis of the pelvis, the cartilaginous joint that strongly unites the right and left hip bones of the pelvis. The cartilaginous joints in which vertebrae are united by intervertebral discs provide for small movements between the adjacent vertebrae and are also an amphiarthrosis type of joint. Thus, based on their movement ability, both fibrous and cartilaginous joints are functionally classified as a synarthrosis or amphiarthrosis.

The most common type of joint is the diarthrosis, which is a freely moveable joint. All synovial joints are functionally classified as diarthroses. A uniaxial diarthrosis, such as the elbow, is a joint that only allows for movement within a single anatomical plane. Joints that allow for movements in two planes are biaxial joints, such as the

metacarpophalangeal joints of the fingers. A multiaxial joint, such as the shoulder or hip joint, allows for three planes of motions.

Review Questions

The joint between adjacent vertebrae that includes an invertebral disc is classified as which type of joint?

1. diarthrosis
2. multiaxial
3. amphiarthrosis
4. synarthrosis

C

Which of these joints is classified as a synarthrosis?

1. the pubic symphysis
2. the manubriosternal joint
3. an invertebral disc
4. the shoulder joint

B

Which of these joints is classified as a biaxial diarthrosis?

1. the metacarpophalangeal joint
2. the hip joint
3. the elbow joint
4. the pubic symphysis

A

Synovial joints ______.

1. may be functionally classified as a synarthrosis
2. are joints where the bones are connected to each other by hyaline cartilage
3. may be functionally classified as a amphiarthrosis
4. are joints where the bones articulate with each other within a fluid-filled joint cavity

---

D

Critical Thinking Questions

Define how joints are classified based on function. Describe and give an example for each functional type of joint.

Functional classification of joints is based on the degree of mobility exhibited by the joint. A synarthrosis is an immobile or nearly immobile joint. An example is the manubriosternal joint or the joints between the skull bones surrounding the brain. An amphiarthrosis is a slightly moveable joint, such as the pubic symphysis or an intervertebral cartilaginous joint. A diarthrosis is a freely moveable joint. These are subdivided into three categories. A uniaxial diarthrosis allows movement within a single anatomical plane or axis of motion. The elbow joint is an example. A biaxial diarthrosis, such as the metacarpophalangeal joint, allows for movement along two planes or axes. The hip and shoulder joints are examples of a multiaxial diarthrosis. These allow movements along three planes or axes.

Explain the reasons for why joints differ in their degree of mobility.

The functional needs of joints vary and thus joints differ in their degree of mobility. A synarthrosis, which is an immobile joint, serves

to strongly connect bones thus protecting internal organs such as the heart or brain. A slightly moveable amphiarthrosis provides for small movements, which in the vertebral column can add together to yield a much larger overall movement. The freedom of movement provided by a diarthrosis can allow for large movements, such as is seen with most joints of the limbs.

Glossary

amphiarthrosis
: slightly mobile joint

articulation
: joint of the body

biaxial joint
: type of diarthrosis; a joint that allows for movements within two planes (two axes)

cartilaginous joint
: joint at which the bones are united by hyaline cartilage (synchondrosis) or fibrocartilage (symphysis)

diarthrosis
: freely mobile joint

fibrous joint

joint where the articulating areas of the adjacent bones are connected by fibrous connective tissue

joint
: site at which two or more bones or bone and cartilage come together (articulate)

joint cavity
: space enclosed by the articular capsule of a synovial joint that is filled with synovial fluid and contains the articulating surfaces of the adjacent bones

multiaxial joint
: type of diarthrosis; a joint that allows for movements within three planes (three axes)

synarthrosis
: immobile or nearly immobile joint

synovial joint
: joint at which the articulating surfaces of the bones are located within a joint cavity formed by an articular capsule

uniaxial joint
: type of diarthrosis; joint that allows for motion within only one plane (one axis)

Introduction
class="introduction"
Tennis Player
Athletes rely on toned skeletal muscles to supply the force required for movement. (credit: Emmanuel Huybrechts/flickr)


Chapter Objectives
After studying this chapter, you will be able to:

- Explain the organization of muscle tissue
- Describe the function and structure of skeletal, cardiac muscle, and smooth muscle
- Explain how muscles work with tendons to move the body
- Describe how muscles contract and relax
- Define the process of muscle metabolism

- Explain how the nervous system controls muscle tension
- Relate the connections between exercise and muscle performance
- Explain the development and regeneration of muscle tissue

When most people think of muscles, they think of the muscles that are visible just under the skin, particularly of the limbs. These are skeletal muscles, so-named because most of them move the skeleton. But there are two other types of muscle in the body, with distinctly different jobs. Cardiac muscle, found in the heart, is concerned with pumping blood through the circulatory system. Smooth muscle is concerned with various involuntary movements, such as having one's hair stand on end when cold or frightened, or moving food through the digestive system. This chapter will examine the structure and function of these three types of muscles.

Overview of Muscle Tissues

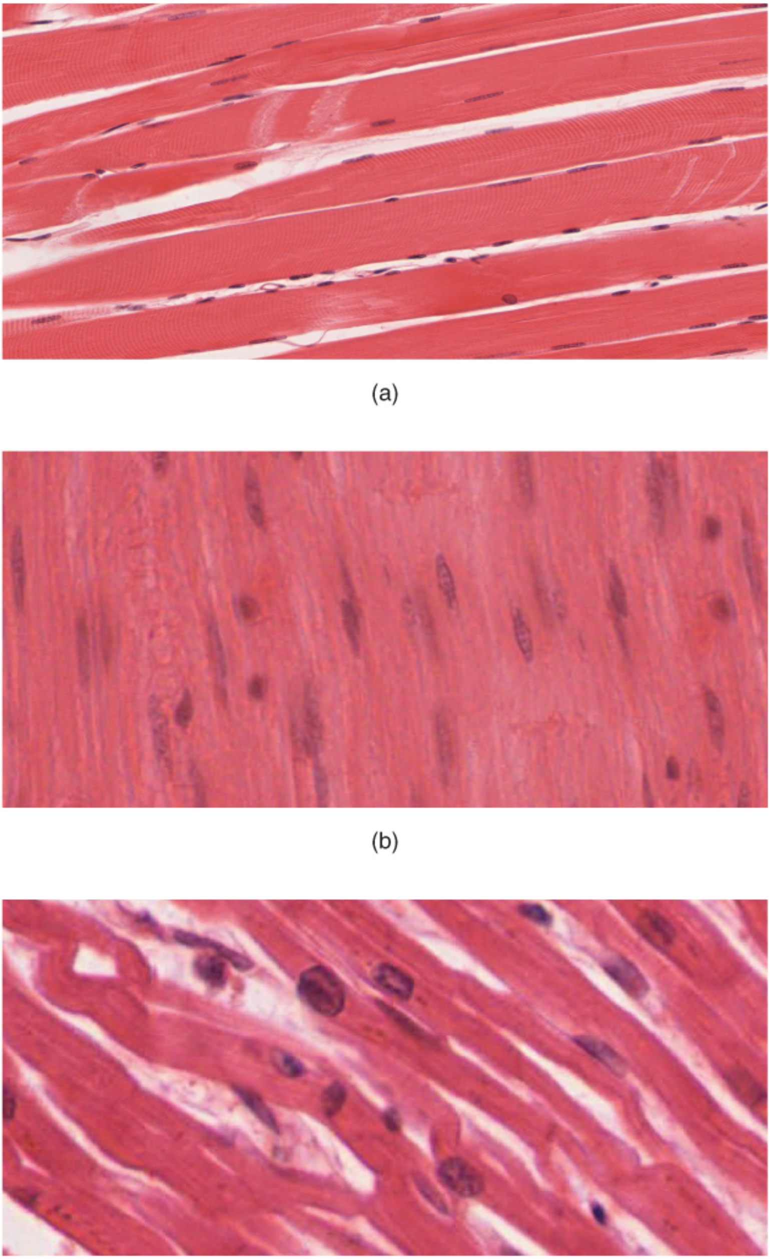
By the end of this section, you will be able to:

- Describe the different types of muscle
- Explain contractibility and extensibility

Muscle is one of the four primary tissue types of the body, and the body contains three types of muscle tissue: skeletal muscle, cardiac muscle, and smooth muscle ([link]). All three muscle tissues have some properties in common; they all exhibit a quality called **excitability** as their plasma membranes can change their electrical states (from polarized to depolarized) and send an electrical wave called an action potential along the entire length of the membrane. While the nervous system can influence the excitability of cardiac and smooth muscle to some degree, skeletal muscle completely depends on signaling from the nervous system to work properly. On the other hand, both cardiac muscle and smooth muscle can respond to other stimuli, such as hormones and local stimuli.

The Three Types of Muscle Tissue

The body contains three types of muscle tissue: (a) skeletal muscle, (b) smooth muscle, and (c) cardiac muscle. From top, LM × 1600, LM × 1600, LM × 1600. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)



(a)

(b)

(c)

The muscles all begin the actual process of

contracting (shortening) when a protein called actin is pulled by a protein called myosin. This occurs in striated muscle (skeletal and cardiac) after specific binding sites on the actin have been exposed in response to the interaction between calcium ions (Ca^{++}) and proteins (troponin and tropomyosin) that "shield" the actin-binding sites. Ca^{++} also is required for the contraction of smooth muscle, although its role is different: here Ca^{++} activates enzymes, which in turn activate myosin heads. All muscles require adenosine triphosphate (ATP) to continue the process of contracting, and they all relax when the Ca^{++} is removed and the actin-binding sites are re-shielded.

A muscle can return to its original length when relaxed due to a quality of muscle tissue called **elasticity**. It can recoil back to its original length due to elastic fibers. Muscle tissue also has the quality of **extensibility**; it can stretch or extend. **Contractility** allows muscle tissue to pull on its attachment points and shorten with force.

Differences among the three muscle types include the microscopic organization of their contractile proteins—actin and myosin. The actin and myosin proteins are arranged very regularly in the cytoplasm of individual muscle cells (referred to as fibers) in both skeletal muscle and cardiac muscle, which creates a pattern, or stripes, called striations. The striations are visible with a light microscope

under high magnification (see [link]). **Skeletal muscle** fibers are multinucleated structures that compose the skeletal muscle. **Cardiac muscle** fibers each have one to two nuclei and are physically and electrically connected to each other so that the entire heart contracts as one unit (called a syncytium).

Because the actin and myosin are not arranged in such regular fashion in **smooth muscle**, the cytoplasm of a smooth muscle fiber (which has only a single nucleus) has a uniform, nonstriated appearance (resulting in the name smooth muscle). However, the less organized appearance of smooth muscle should not be interpreted as less efficient. Smooth muscle in the walls of arteries is a critical component that regulates blood pressure necessary to push blood through the circulatory system; and smooth muscle in the skin, visceral organs, and internal passageways is essential for moving all materials through the body.

Chapter Review

Muscle is the tissue in animals that allows for active movement of the body or materials within the body. There are three types of muscle tissue: skeletal muscle, cardiac muscle, and smooth muscle. Most of the body's skeletal muscle produces movement by acting on the skeleton. Cardiac muscle is found in

the wall of the heart and pumps blood through the circulatory system.

Smooth muscle is found in the skin, where it is associated with hair follicles; it also is found in the walls of internal organs, blood vessels, and internal passageways, where it assists in moving materials.

Review Questions

Muscle that has a striped appearance is described as being ______.

1. elastic
2. nonstriated
3. excitable
4. striated

D

Which element is important in directly triggering contraction?

1. sodium (Na^+)
2. calcium (Ca^{++})
3. potassium (K^+)
4. chloride (Cl^-)

B

Which of the following properties is *not* common to all three muscle tissues?

1. excitability
2. the need for ATP
3. at rest, uses shielding proteins to cover actin-binding sites
4. elasticity

C

Critical Thinking Questions

Why is elasticity an important quality of muscle tissue?

It allows muscle to return to its original length during relaxation after contraction.

Glossary

cardiac muscle

striated muscle found in the heart; joined to one another at intercalated discs and under the regulation of pacemaker cells, which contract as one unit to pump blood through the circulatory system. Cardiac muscle is under involuntary control.

contractility
: ability to shorten (contract) forcibly

elasticity
: ability to stretch and rebound

excitability
: ability to undergo neural stimulation

extensibility
: ability to lengthen (extend)

skeletal muscle
: striated, multinucleated muscle that requires signaling from the nervous system to trigger contraction; most skeletal muscles are referred to as voluntary muscles that move bones and produce movement

smooth muscle
: nonstriated, mononucleated muscle in the skin that is associated with hair follicles; assists in moving materials in the walls of internal organs, blood vessels, and internal passageways

Skeletal Muscle

By the end of this section, you will be able to:

- Describe the layers of connective tissues packaging skeletal muscle
- Explain how muscles work with tendons to move the body
- Identify areas of the skeletal muscle fibers
- Describe excitation-contraction coupling

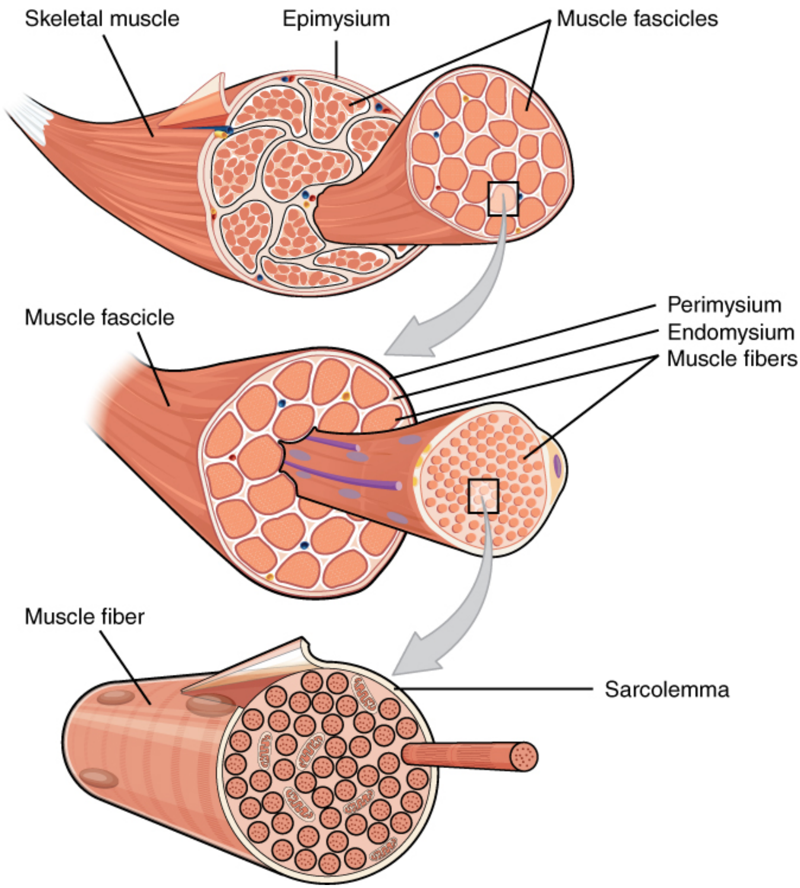
The best-known feature of skeletal muscle is its ability to contract and cause movement. Skeletal muscles act not only to produce movement but also to stop movement, such as resisting gravity to maintain posture. Small, constant adjustments of the skeletal muscles are needed to hold a body upright or balanced in any position. Muscles also prevent excess movement of the bones and joints, maintaining skeletal stability and preventing skeletal structure damage or deformation. Joints can become misaligned or dislocated entirely by pulling on the associated bones; muscles work to keep joints stable. Skeletal muscles are located throughout the body at the openings of internal tracts to control the movement of various substances. These muscles allow functions, such as swallowing, urination, and defecation, to be under voluntary control. Skeletal muscles also protect internal organs (particularly abdominal and pelvic organs) by acting as an external barrier or shield to external trauma and by supporting the weight of the organs.

Skeletal muscles contribute to the maintenance of homeostasis in the body by generating heat. Muscle contraction requires energy, and when ATP is broken down, heat is produced. This heat is very noticeable during exercise, when sustained muscle movement causes body temperature to rise, and in cases of extreme cold, when shivering produces random skeletal muscle contractions to generate heat.

Each skeletal muscle is an organ that consists of various integrated tissues. These tissues include the skeletal muscle fibers, blood vessels, nerve fibers, and connective tissue. Each skeletal muscle has three layers of connective tissue (called “mysia”) that enclose it and provide structure to the muscle as a whole, and also compartmentalize the muscle fibers within the muscle ([link]). Each muscle is wrapped in a sheath of dense, irregular connective tissue called the **epimysium**, which allows a muscle to contract and move powerfully while maintaining its structural integrity. The epimysium also separates muscle from other tissues and organs in the area, allowing the muscle to move independently.

The Three Connective Tissue Layers

Bundles of muscle fibers, called fascicles, are covered by the perimysium. Muscle fibers are covered by the endomysium.



Inside each skeletal muscle, muscle fibers are organized into individual bundles, each called a **fascicle**, by a middle layer of connective tissue called the **perimysium**. This fascicular organization is common in muscles of the limbs; it allows the nervous system to trigger a specific movement of a muscle by activating a subset of muscle fibers within a bundle, or fascicle of the muscle. Inside each fascicle, each muscle fiber is encased in a thin connective tissue layer of collagen and reticular fibers called the **endomysium**. The endomysium

contains the extracellular fluid and nutrients to support the muscle fiber. These nutrients are supplied via blood to the muscle tissue.

In skeletal muscles that work with tendons to pull on bones, the collagen in the three tissue layers (the mysia) intertwines with the collagen of a tendon. At the other end of the tendon, it fuses with the periosteum coating the bone. The tension created by contraction of the muscle fibers is then transferred though the mysia, to the tendon, and then to the periosteum to pull on the bone for movement of the skeleton. In other places, the mysia may fuse with a broad, tendon-like sheet called an **aponeurosis**, or to fascia, the connective tissue between skin and bones. The broad sheet of connective tissue in the lower back that the latissimus dorsi muscles (the “lats”) fuse into is an example of an aponeurosis.

Every skeletal muscle is also richly supplied by blood vessels for nourishment, oxygen delivery, and waste removal. In addition, every muscle fiber in a skeletal muscle is supplied by the axon branch of a somatic motor neuron, which signals the fiber to contract. Unlike cardiac and smooth muscle, the only way to functionally contract a skeletal muscle is through signaling from the nervous system.

Skeletal Muscle Fibers

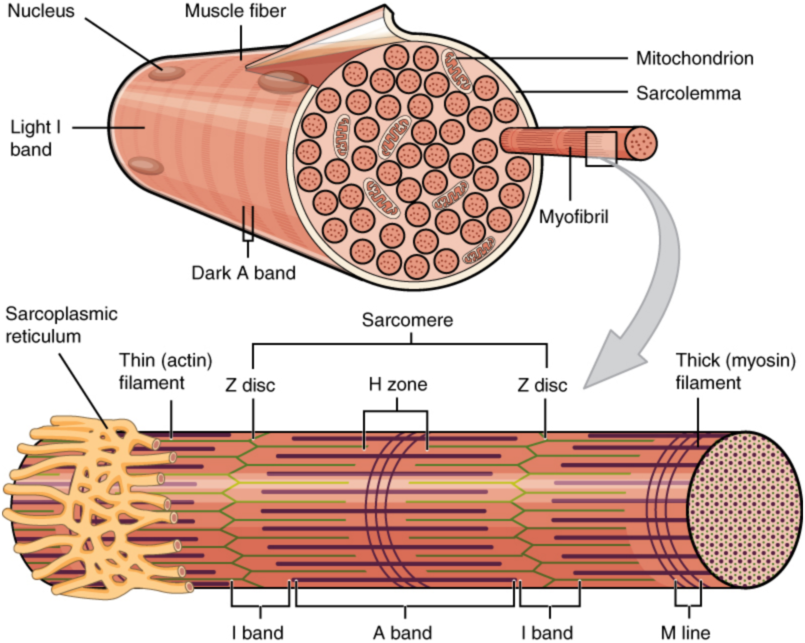
Because skeletal muscle cells are long and cylindrical, they are commonly referred to as muscle fibers. Skeletal muscle fibers can be quite large for human cells, with diameters up to 100 μm and lengths up to 30 cm (11.8 in) in the Sartorius of the upper leg. During early development, embryonic myoblasts, each with its own nucleus, fuse with up to hundreds of other myoblasts to form the multinucleated skeletal muscle fibers. Multiple nuclei mean multiple copies of genes, permitting the production of the large amounts of proteins and enzymes needed for muscle contraction.

Some other terminology associated with muscle fibers is rooted in the Greek *sarco*, which means "flesh." The plasma membrane of muscle fibers is called the **sarcolemma**, the cytoplasm is referred to as **sarcoplasm**, and the specialized smooth endoplasmic reticulum, which stores, releases, and retrieves calcium ions (Ca^{++}) is called the **sarcoplasmic reticulum (SR)** ([link]). As will soon be described, the functional unit of a skeletal muscle fiber is the sarcomere, a highly organized arrangement of the contractile myofilaments **actin** (thin filament) and **myosin** (thick filament), along with other support proteins.

Muscle Fiber

A skeletal muscle fiber is surrounded by a plasma membrane called the sarcolemma, which contains sarcoplasm, the cytoplasm of muscle cells. A muscle fiber is composed of many fibrils, which give the

cell its striated appearance.



The Sarcomere

The striated appearance of skeletal muscle fibers is due to the arrangement of the myofilaments of actin and myosin in sequential order from one end of the muscle fiber to the other. Each packet of these microfilaments and their regulatory proteins, **troponin** and **tropomyosin** (along with other proteins) is called a **sarcomere**.

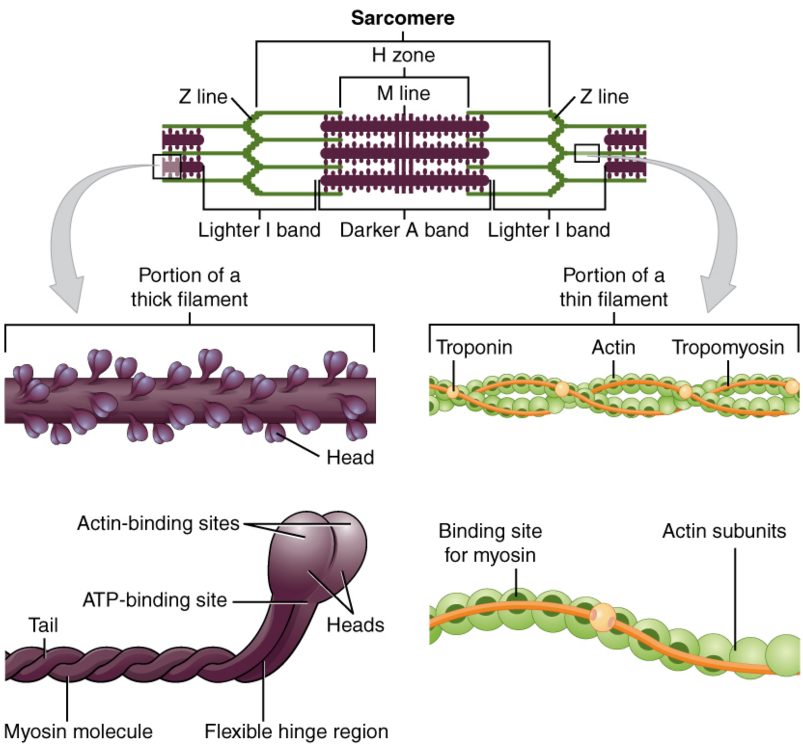
Watch this video to learn more about macro- and microstructures of skeletal muscles. (a) What are the names of the "junction points" between sarcomeres? (b) What are the names of the "subunits" within the myofibrils that run the length of skeletal muscle fibers? (c) What is the "double strand of pearls" described in the video? (d) What gives a skeletal muscle fiber its striated appearance?

The sarcomere is the functional unit of the muscle fiber. The sarcomere itself is bundled within the myofibril that runs the entire length of the muscle fiber and attaches to the sarcolemma at its end. As myofibrils contract, the entire muscle cell contracts. Because myofibrils are only approximately 1.2 μm in diameter, hundreds to thousands (each with thousands of sarcomeres) can be found inside one muscle fiber. Each sarcomere is approximately 2 μm in length with a three-dimensional cylinder-like arrangement and is bordered by structures called Z-discs (also called Z-lines, because pictures are two-dimensional), to which the actin myofilaments are

anchored ([link]). Because the actin and its troponin-tropomyosin complex (projecting from the Z-discs toward the center of the sarcomere) form strands that are thinner than the myosin, it is called the **thin filament** of the sarcomere. Likewise, because the myosin strands and their multiple heads (projecting from the center of the sarcomere, toward but not all to way to, the Z-discs) have more mass and are thicker, they are called the **thick filament** of the sarcomere.

The Sarcomere

The sarcomere, the region from one Z-line to the next Z-line, is the functional unit of a skeletal muscle fiber.



The Neuromuscular Junction

Another specialization of the skeletal muscle is the site where a motor neuron's terminal meets the muscle fiber—called the **neuromuscular junction (NMJ)**. This is where the muscle fiber first responds to signaling by the motor neuron. Every skeletal muscle fiber in every skeletal muscle is innervated by a motor neuron at the NMJ. Excitation signals from the neuron are the only way to functionally activate the fiber to contract.

Every skeletal muscle fiber is supplied by a motor neuron at the NMJ. Watch this video to learn more about what happens at the NMJ. (a) What is the definition of a motor unit? (b) What is the structural and functional difference between a large motor unit and a small motor unit? (c) Can you give an example of each? (d) Why is the neurotransmitter acetylcholine degraded after binding to its receptor?

Excitation-Contraction Coupling

All living cells have membrane potentials, or electrical gradients across their membranes. The inside of the membrane is usually around -60 to -90 mV, relative to the outside. This is referred to as a cell's membrane potential. Neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction.

Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

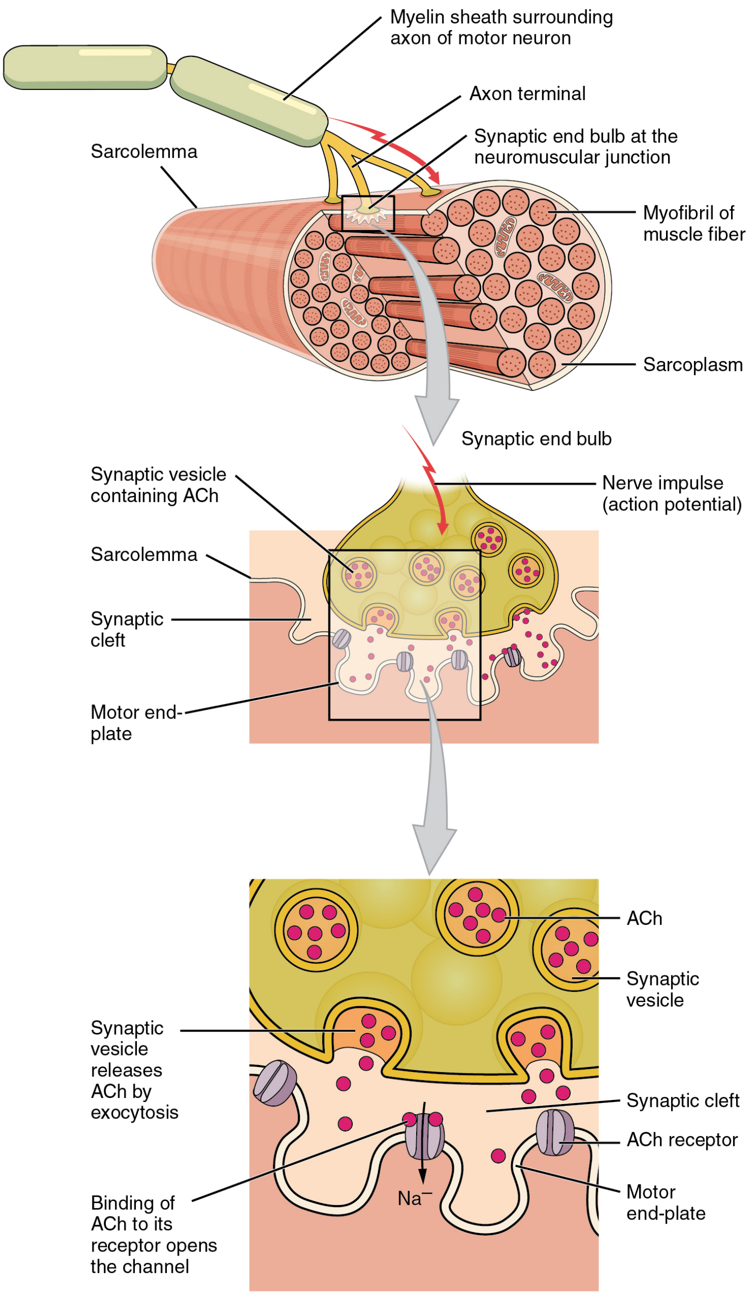
Although the term **excitation-contraction coupling** confuses or scares some students, it comes down to this: for a skeletal muscle fiber to contract,

its membrane must first be “excited”—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the sarcolemma as a wave, is “coupled” to the actual contraction through the release of calcium ions (Ca^{++}) from the SR. Once released, the Ca^{++} interacts with the shielding proteins, forcing them to move aside so that the actin-binding sites are available for attachment by myosin heads. The myosin then pulls the actin filaments toward the center, shortening the muscle fiber.

In skeletal muscle, this sequence begins with signals from the somatic motor division of the nervous system. In other words, the “excitation” step in skeletal muscles is always triggered by signaling from the nervous system ([link]).

Motor End-Plate and Innervation

At the NMJ, the axon terminal releases ACh. The motor end-plate is the location of the ACh-receptors in the muscle fiber sarcolemma. When ACh molecules are released, they diffuse across a minute space called the synaptic cleft and bind to the receptors.



The motor neurons that tell the skeletal muscle

fibers to contract originate in the spinal cord, with a smaller number located in the brainstem for activation of skeletal muscles of the face, head, and neck. These neurons have long processes, called axons, which are specialized to transmit action potentials long distances— in this case, all the way from the spinal cord to the muscle itself (which may be up to three feet away). The axons of multiple neurons bundle together to form nerves, like wires bundled together in a cable.

Signaling begins when a neuronal **action potential** travels along the axon of a motor neuron, and then along the individual branches to terminate at the NMJ. At the NMJ, the axon terminal releases a chemical messenger, or **neurotransmitter**, called **acetylcholine (ACh)**. The ACh molecules diffuse across a minute space called the **synaptic cleft** and bind to ACh receptors located within the **motor end-plate** of the sarcolemma on the other side of the synapse. Once ACh binds, a channel in the ACh receptor opens and positively charged ions can pass through into the muscle fiber, causing it to **depolarize**, meaning that the membrane potential of the muscle fiber becomes less negative (closer to zero.)

As the membrane depolarizes, another set of ion channels called **voltage-gated sodium channels** are triggered to open. Sodium ions enter the muscle fiber, and an action potential rapidly spreads (or

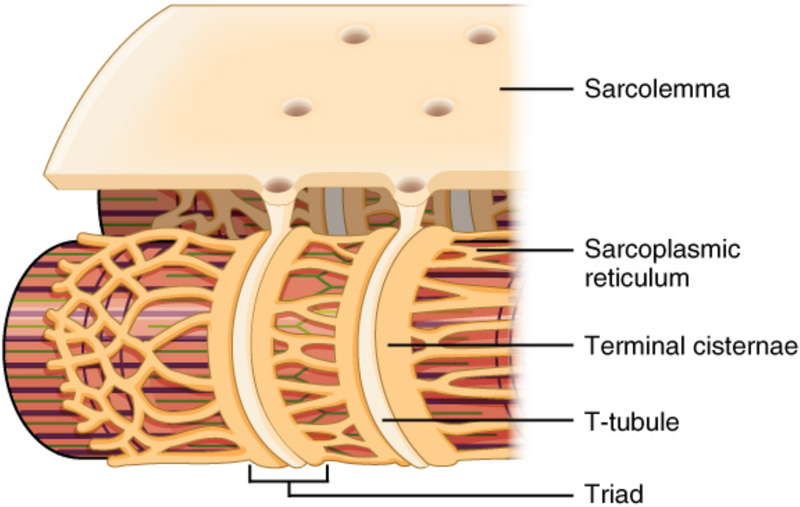
“fires”) along the entire membrane to initiate excitation-contraction coupling.

Things happen very quickly in the world of excitable membranes (just think about how quickly you can snap your fingers as soon as you decide to do it). Immediately following depolarization of the membrane, it repolarizes, re-establishing the negative membrane potential. Meanwhile, the ACh in the synaptic cleft is degraded by the enzyme acetylcholinesterase (AChE) so that the ACh cannot rebind to a receptor and reopen its channel, which would cause unwanted extended muscle excitation and contraction.

Propagation of an action potential along the sarcolemma is the excitation portion of excitation-contraction coupling. Recall that this excitation actually triggers the release of calcium ions (Ca^{++}) from its storage in the cell’s SR. For the action potential to reach the membrane of the SR, there are periodic invaginations in the sarcolemma, called **T-tubules** (“T” stands for “transverse”). You will recall that the diameter of a muscle fiber can be up to 100 μm, so these T-tubules ensure that the membrane can get close to the SR in the sarcoplasm. The arrangement of a T-tubule with the membranes of SR on either side is called a **triad** ([link]). The triad surrounds the cylindrical structure called a **myofibril**, which contains actin and myosin.

The T-tubule

Narrow T-tubules permit the conduction of electrical impulses. The SR functions to regulate intracellular levels of calcium. Two terminal cisternae (where enlarged SR connects to the T-tubule) and one T-tubule comprise a triad—a “threesome” of membranes, with those of SR on two sides and the T-tubule sandwiched between them.



The T-tubules carry the action potential into the interior of the cell, which triggers the opening of calcium channels in the membrane of the adjacent SR, causing Ca^{++} to diffuse out of the SR and into the sarcoplasm. It is the arrival of Ca^{++} in the sarcoplasm that initiates contraction of the muscle fiber by its contractile units, or sarcomeres.

Chapter Review

Skeletal muscles contain connective tissue, blood vessels, and nerves. There are three layers of connective tissue: epimysium, perimysium, and endomysium. Skeletal muscle fibers are organized into groups called fascicles. Blood vessels and nerves enter the connective tissue and branch in the cell. Muscles attach to bones directly or through tendons or aponeuroses. Skeletal muscles maintain posture, stabilize bones and joints, control internal movement, and generate heat.

Skeletal muscle fibers are long, multinucleated cells. The membrane of the cell is the sarcolemma; the cytoplasm of the cell is the sarcoplasm. The sarcoplasmic reticulum (SR) is a form of endoplasmic reticulum. Muscle fibers are composed of myofibrils. The striations are created by the organization of actin and myosin resulting in the banding pattern of myofibrils.

Interactive Link Questions

Watch this video to learn more about macro- and microstructures of skeletal muscles. (a) What are the names of the “junction points” between sarcomeres? (b) What are the names of the “subunits” within the myofibrils that run the length of skeletal muscle fibers? (c) What is

the “double strand of pearls” described in the video? (d) What gives a skeletal muscle fiber its striated appearance?

(a) Z-lines. (b) Sarcomeres. (c) This is the arrangement of the actin and myosin filaments in a sarcomere. (d) The alternating strands of actin and myosin filaments.

Every skeletal muscle fiber is supplied by a motor neuron at the NMJ. Watch this video to learn more about what happens at the neuromuscular junction. (a) What is the definition of a motor unit? (b) What is the structural and functional difference between a large motor unit and a small motor unit? Can you give an example of each? (c) Why is the neurotransmitter acetylcholine degraded after binding to its receptor?

(a) It is the number of skeletal muscle fibers supplied by a single motor neuron. (b) A large motor unit has one neuron supplying many skeletal muscle fibers for gross movements, like the Temporalis muscle, where 1000 fibers are supplied by one neuron. A small motor has one neuron supplying few skeletal muscle fibers for very fine movements, like the extraocular eye muscles, where six fibers are supplied by one

neuron. (c) To avoid prolongation of muscle contraction.

Review Questions

The correct order for the smallest to the largest unit of organization in muscle tissue is _____.

1. fascicle, filament, muscle fiber, myofibril
2. filament, myofibril, muscle fiber, fascicle
3. muscle fiber, fascicle, filament, myofibril
4. myofibril, muscle fiber, filament, fascicle

B

Depolarization of the sarcolemma means _____.

1. the inside of the membrane has become less negative as sodium ions accumulate
2. the outside of the membrane has become less negative as sodium ions accumulate
3. the inside of the membrane has become more negative as sodium ions accumulate
4. the sarcolemma has completely lost any electrical charge

A

Critical Thinking Questions

What would happen to skeletal muscle if the epimysium were destroyed?

Muscles would lose their integrity during powerful movements, resulting in muscle damage.

Describe how tendons facilitate body movement.

When a muscle contracts, the force of movement is transmitted through the tendon, which pulls on the bone to produce skeletal movement.

What are the five primary functions of skeletal muscle?

Produce movement of the skeleton, maintain posture and body position, support soft tissues,

encircle openings of the digestive, urinary, and other tracts, and maintain body temperature.

What are the opposite roles of voltage-gated sodium channels and voltage-gated potassium channels?

The opening of voltage-gated sodium channels, followed by the influx of Na^+, transmits an Action Potential after the membrane has sufficiently depolarized. The delayed opening of potassium channels allows K^+ to exit the cell, to repolarize the membrane.

Glossary

acetylcholine (ACh)
: neurotransmitter that binds at a motor end-plate to trigger depolarization

actin
: protein that makes up most of the thin myofilaments in a sarcomere muscle fiber

action potential
: change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers

aponeurosis
: broad, tendon-like sheet of connective tissue that attaches a skeletal muscle to another skeletal muscle or to a bone

depolarize
: to reduce the voltage difference between the inside and outside of a cell’s plasma membrane (the sarcolemma for a muscle fiber), making the inside less negative than at rest

endomysium
: loose, and well-hydrated connective tissue covering each muscle fiber in a skeletal muscle

epimysium
: outer layer of connective tissue around a skeletal muscle

excitation-contraction coupling
: sequence of events from motor neuron signaling to a skeletal muscle fiber to contraction of the fiber’s sarcomeres

fascicle
: bundle of muscle fibers within a skeletal muscle

motor end-plate
: sarcolemma of muscle fiber at the

neuromuscular junction, with receptors for the neurotransmitter acetylcholine

myofibril
: long, cylindrical organelle that runs parallel within the muscle fiber and contains the sarcomeres

myosin
: protein that makes up most of the thick cylindrical myofilament within a sarcomere muscle fiber

neuromuscular junction (NMJ)
: synapse between the axon terminal of a motor neuron and the section of the membrane of a muscle fiber with receptors for the acetylcholine released by the terminal

neurotransmitter
: signaling chemical released by nerve terminals that bind to and activate receptors on target cells

perimysium
: connective tissue that bundles skeletal muscle fibers into fascicles within a skeletal muscle

sarcomere
: longitudinally, repeating functional unit of skeletal muscle, with all of the contractile and associated proteins involved in contraction

sarcolemma

plasma membrane of a skeletal muscle fiber

sarcoplasm

cytoplasm of a muscle cell

sarcoplasmic reticulum (SR)

specialized smooth endoplasmic reticulum, which stores, releases, and retrieves Ca^{++}

synaptic cleft

space between a nerve (axon) terminal and a motor end-plate

T-tubule

projection of the sarcolemma into the interior of the cell

thick filament

the thick myosin strands and their multiple heads projecting from the center of the sarcomere toward, but not all to way to, the Z-discs

thin filament

thin strands of actin and its troponin-tropomyosin complex projecting from the Z-discs toward the center of the sarcomere

triad

the grouping of one T-tubule and two terminal cisternae

troponin

regulatory protein that binds to actin, tropomyosin, and calcium

tropomyosin

regulatory protein that covers myosin-binding sites to prevent actin from binding to myosin

voltage-gated sodium channels

membrane proteins that open sodium channels in response to a sufficient voltage change, and initiate and transmit the action potential as Na^+ enters through the channel

Types of Muscle Fibers

By the end of this section, you will be able to:

- Describe the types of skeletal muscle fibers
- Explain fast and slow muscle fibers

Two criteria to consider when classifying the types of muscle fibers are how fast some fibers contract relative to others, and how fibers produce ATP. Using these criteria, there are three main types of skeletal muscle fibers. **Slow oxidative (SO)** fibers contract relatively slowly and use aerobic respiration (oxygen and glucose) to produce ATP. **Fast oxidative (FO)** fibers have fast contractions and primarily use aerobic respiration, but because they may switch to anaerobic respiration (glycolysis), can fatigue more quickly than SO fibers. Lastly, **fast glycolytic (FG)** fibers have fast contractions and primarily use anaerobic glycolysis. The FG fibers fatigue more quickly than the others. Most skeletal muscles in a human contain(s) all three types, although in varying proportions.

The speed of contraction is dependent on how quickly myosin's ATPase hydrolyzes ATP to produce cross-bridge action. Fast fibers hydrolyze ATP approximately twice as quickly as slow fibers, resulting in much quicker cross-bridge cycling (which pulls the thin filaments toward the center of the sarcomeres at a faster rate). The primary metabolic pathway used by a muscle fiber

determines whether the fiber is classified as oxidative or glycolytic. If a fiber primarily produces ATP through aerobic pathways it is oxidative. More ATP can be produced during each metabolic cycle, making the fiber more resistant to fatigue. Glycolytic fibers primarily create ATP through anaerobic glycolysis, which produces less ATP per cycle. As a result, glycolytic fibers fatigue at a quicker rate.

The oxidative fibers contain many more mitochondria than the glycolytic fibers, because aerobic metabolism, which uses oxygen (O_2) in the metabolic pathway, occurs in the mitochondria. The SO fibers possess a large number of mitochondria and are capable of contracting for longer periods because of the large amount of ATP they can produce, but they have a relatively small diameter and do not produce a large amount of tension. SO fibers are extensively supplied with blood capillaries to supply O_2 from the red blood cells in the bloodstream. The SO fibers also possess myoglobin, an O_2-carrying molecule similar to O_2-carrying hemoglobin in the red blood cells. The myoglobin stores some of the needed O_2 within the fibers themselves (and gives SO fibers their red color). All of these features allow SO fibers to produce large quantities of ATP, which can sustain muscle activity without fatiguing for long periods of time.

The fact that SO fibers can function for long periods

without fatiguing makes them useful in maintaining posture, producing isometric contractions, stabilizing bones and joints, and making small movements that happen often but do not require large amounts of energy. They do not produce high tension, and thus they are not used for powerful, fast movements that require high amounts of energy and rapid cross-bridge cycling.

FO fibers are sometimes called intermediate fibers because they possess characteristics that are intermediate between fast fibers and slow fibers. They produce ATP relatively quickly, more quickly than SO fibers, and thus can produce relatively high amounts of tension. They are oxidative because they produce ATP aerobically, possess high amounts of mitochondria, and do not fatigue quickly. However, FO fibers do not possess significant myoglobin, giving them a lighter color than the red SO fibers. FO fibers are used primarily for movements, such as walking, that require more energy than postural control but less energy than an explosive movement, such as sprinting. FO fibers are useful for this type of movement because they produce more tension than SO fibers but they are more fatigue-resistant than FG fibers.

FG fibers primarily use anaerobic glycolysis as their ATP source. They have a large diameter and possess high amounts of glycogen, which is used in glycolysis to generate ATP quickly to produce high

levels of tension. Because they do not primarily use aerobic metabolism, they do not possess substantial numbers of mitochondria or significant amounts of myoglobin and therefore have a white color. FG fibers are used to produce rapid, forceful contractions to make quick, powerful movements. These fibers fatigue quickly, permitting them to only be used for short periods. Most muscles possess a mixture of each fiber type. The predominant fiber type in a muscle is determined by the primary function of the muscle.

Chapter Review

ATP provides the energy for muscle contraction. The three mechanisms for ATP regeneration are creatine phosphate, anaerobic glycolysis, and aerobic metabolism. Creatine phosphate provides about the first 15 seconds of ATP at the beginning of muscle contraction. Anaerobic glycolysis produces small amounts of ATP in the absence of oxygen for a short period. Aerobic metabolism utilizes oxygen to produce much more ATP, allowing a muscle to work for longer periods. Muscle fatigue, which has many contributing factors, occurs when muscle can no longer contract. An oxygen debt is created as a result of muscle use. The three types of muscle fiber are slow oxidative (SO), fast oxidative (FO) and fast glycolytic (FG). SO fibers use aerobic metabolism to produce low power contractions over long periods

and are slow to fatigue. FO fibers use aerobic metabolism to produce ATP but produce higher tension contractions than SO fibers. FG fibers use anaerobic metabolism to produce powerful, high-tension contractions but fatigue quickly.

Review Questions

Muscle fatigue is caused by _____.

1. buildup of ATP and lactic acid levels
2. exhaustion of energy reserves and buildup of lactic acid levels
3. buildup of ATP and pyruvic acid levels
4. exhaustion of energy reserves and buildup of pyruvic acid levels

---

B

A sprinter would experience muscle fatigue sooner than a marathon runner due to _____.

1. anaerobic metabolism in the muscles of the sprinter
2. anaerobic metabolism in the muscles of the marathon runner
3. aerobic metabolism in the muscles of the

sprinter
4. glycolysis in the muscles of the marathon runner

A

What aspect of creatine phosphate allows it to supply energy to muscles?

1. ATPase activity
2. phosphate bonds
3. carbon bonds
4. hydrogen bonds

B

Drug X blocks ATP regeneration from ADP and phosphate. How will muscle cells respond to this drug?

1. by absorbing ATP from the bloodstream
2. by using ADP as an energy source
3. by using glycogen as an energy source
4. none of the above

D

Critical Thinking Questions

Why do muscle cells use creatine phosphate instead of glycolysis to supply ATP for the first few seconds of muscle contraction?

Creatine phosphate is used because creatine phosphate and ADP are converted very quickly into ATP by creatine kinase. Glycolysis cannot generate ATP as quickly as creatine phosphate.

Is aerobic respiration more or less efficient than glycolysis? Explain your answer.

Aerobic respiration is much more efficient than anaerobic glycolysis, yielding 36 ATP per molecule of glucose, as opposed to two ATP produced by glycolysis.

Glossary

fast glycolytic (FG)
: muscle fiber that primarily uses anaerobic glycolysis

fast oxidative (FO)

intermediate muscle fiber that is between slow oxidative and fast glycolytic fibers

slow oxidative (SO)
: muscle fiber that primarily uses aerobic respiration

Exercise and Muscle Performance
By the end of this section, you will be able to:

- Describe hypertrophy and atrophy
- Explain how resistance exercise builds muscle
- Explain how performance-enhancing substances affect muscle

Physical training alters the appearance of skeletal muscles and can produce changes in muscle performance. Conversely, a lack of use can result in decreased performance and muscle appearance. Although muscle cells can change in size, new cells are not formed when muscles grow. Instead, structural proteins are added to muscle fibers in a process called **hypertrophy**, so cell diameter increases. The reverse, when structural proteins are lost and muscle mass decreases, is called **atrophy**. Age-related muscle atrophy is called **sarcopenia**. Cellular components of muscles can also undergo changes in response to changes in muscle use.

Endurance Exercise

Slow fibers are predominantly used in endurance exercises that require little force but involve numerous repetitions. The aerobic metabolism used by slow-twitch fibers allows them to maintain contractions over long periods. Endurance training

modifies these slow fibers to make them even more efficient by producing more mitochondria to enable more aerobic metabolism and more ATP production. Endurance exercise can also increase the amount of myoglobin in a cell, as increased aerobic respiration increases the need for oxygen. Myoglobin is found in the sarcoplasm and acts as an oxygen storage supply for the mitochondria.

The training can trigger the formation of more extensive capillary networks around the fiber, a process called **angiogenesis**, to supply oxygen and remove metabolic waste. To allow these capillary networks to supply the deep portions of the muscle, muscle mass does not greatly increase in order to maintain a smaller area for the diffusion of nutrients and gases. All of these cellular changes result in the ability to sustain low levels of muscle contractions for greater periods without fatiguing.

The proportion of SO muscle fibers in muscle determines the suitability of that muscle for endurance, and may benefit those participating in endurance activities. Postural muscles have a large number of SO fibers and relatively few FO and FG fibers, to keep the back straight ([link]). Endurance athletes, like marathon-runners also would benefit from a larger proportion of SO fibers, but it is unclear if the most-successful marathoners are those with naturally high numbers of SO fibers, or whether the most successful marathon runners

develop high numbers of SO fibers with repetitive training. Endurance training can result in overuse injuries such as stress fractures and joint and tendon inflammation.

Marathoners

Long-distance runners have a large number of SO fibers and relatively few FO and FG fibers. (credit: “Tseo2”/Wikimedia Commons)

Resistance Exercise

Resistance exercises, as opposed to endurance exercise, require large amounts of FG fibers to produce short, powerful movements that are not repeated over long periods. The high rates of ATP hydrolysis and cross-bridge formation in FG fibers result in powerful muscle contractions. Muscles used

for power have a higher ratio of FG to SO/FO fibers, and trained athletes possess even higher levels of FG fibers in their muscles. Resistance exercise affects muscles by increasing the formation of myofibrils, thereby increasing the thickness of muscle fibers. This added structure causes hypertrophy, or the enlargement of muscles, exemplified by the large skeletal muscles seen in body builders and other athletes ([link]). Because this muscular enlargement is achieved by the addition of structural proteins, athletes trying to build muscle mass often ingest large amounts of protein.

Hypertrophy

Body builders have a large number of FG fibers and relatively few FO and SO fibers. (credit: Lin Mei/ flickr)

Except for the hypertrophy that follows an increase in the number of sarcomeres and myofibrils in a

skeletal muscle, the cellular changes observed during endurance training do not usually occur with resistance training. There is usually no significant increase in mitochondria or capillary density. However, resistance training does increase the development of connective tissue, which adds to the overall mass of the muscle and helps to contain muscles as they produce increasingly powerful contractions. Tendons also become stronger to prevent tendon damage, as the force produced by muscles is transferred to tendons that attach the muscle to bone.

For effective strength training, the intensity of the exercise must continually be increased. For instance, continued weight lifting without increasing the weight of the load does not increase muscle size. To produce ever-greater results, the weights lifted must become increasingly heavier, making it more difficult for muscles to move the load. The muscle then adapts to this heavier load, and an even heavier load must be used if even greater muscle mass is desired.

If done improperly, resistance training can lead to overuse injuries of the muscle, tendon, or bone. These injuries can occur if the load is too heavy or if the muscles are not given sufficient time between workouts to recover or if joints are not aligned properly during the exercises. Cellular damage to muscle fibers that occurs after intense exercise

includes damage to the sarcolemma and myofibrils. This muscle damage contributes to the feeling of soreness after strenuous exercise, but muscles gain mass as this damage is repaired, and additional structural proteins are added to replace the damaged ones. Overworking skeletal muscles can also lead to tendon damage and even skeletal damage if the load is too great for the muscles to bear.

Performance-Enhancing Substances

Some athletes attempt to boost their performance by using various agents that may enhance muscle performance. Anabolic steroids are one of the more widely known agents used to boost muscle mass and increase power output. Anabolic steroids are a form of testosterone, a male sex hormone that stimulates muscle formation, leading to increased muscle mass.

Endurance athletes may also try to boost the availability of oxygen to muscles to increase aerobic respiration by using substances such as erythropoietin (EPO), a hormone normally produced in the kidneys, which triggers the production of red blood cells. The extra oxygen carried by these blood cells can then be used by muscles for aerobic respiration. Human growth hormone (hGH) is another supplement, and although it can facilitate building muscle mass, its main role is to promote

the healing of muscle and other tissues after strenuous exercise. Increased hGH may allow for faster recovery after muscle damage, reducing the rest required after exercise, and allowing for more sustained high-level performance.

Although performance-enhancing substances often do improve performance, most are banned by governing bodies in sports and are illegal for nonmedical purposes. Their use to enhance performance raises ethical issues of cheating because they give users an unfair advantage over nonusers. A greater concern, however, is that their use carries serious health risks. The side effects of these substances are often significant, nonreversible, and in some cases fatal. The physiological strain caused by these substances is often greater than what the body can handle, leading to effects that are unpredictable and dangerous. Anabolic steroid use has been linked to infertility, aggressive behavior, cardiovascular disease, and brain cancer.

Similarly, some athletes have used creatine to increase power output. Creatine phosphate provides quick bursts of ATP to muscles in the initial stages of contraction. Increasing the amount of creatine available to cells is thought to produce more ATP and therefore increase explosive power output, although its effectiveness as a supplement has been questioned.

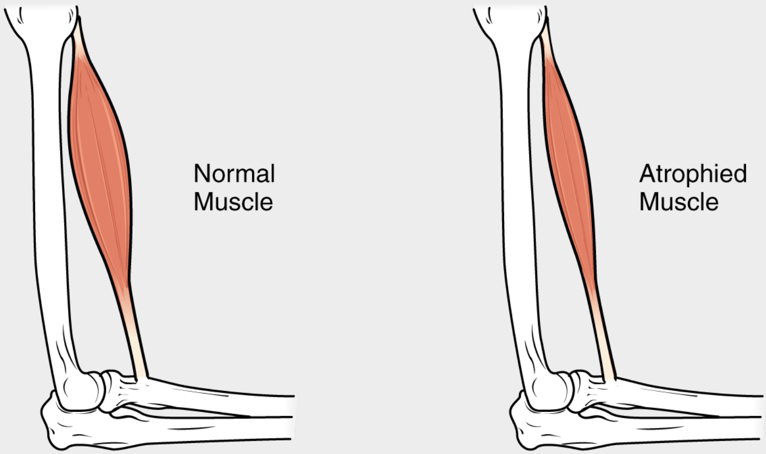
Everyday Connection

Aging and Muscle Tissue

Although atrophy due to disuse can often be reversed with exercise, muscle atrophy with age, referred to as sarcopenia, is irreversible. This is a primary reason why even highly trained athletes succumb to declining performance with age. This decline is noticeable in athletes whose sports require strength and powerful movements, such as sprinting, whereas the effects of age are less noticeable in endurance athletes such as marathon runners or long-distance cyclists. As muscles age, muscle fibers die, and they are replaced by connective tissue and adipose tissue ([link]). Because those tissues cannot contract and generate force as muscle can, muscles lose the ability to produce powerful contractions. The decline in muscle mass causes a loss of strength, including the strength required for posture and mobility. This may be caused by a reduction in FG fibers that hydrolyze ATP quickly to produce short, powerful contractions. Muscles in older people sometimes possess greater numbers of SO fibers, which are responsible for longer contractions and do not produce powerful movements. There may also be a reduction in the size of motor units, resulting in fewer fibers being stimulated and less muscle tension being produced.

Atrophy

Muscle mass is reduced as muscles atrophy with disuse.



Sarcopenia can be delayed to some extent by exercise, as training adds structural proteins and causes cellular changes that can offset the effects of atrophy. Increased exercise can produce greater numbers of cellular mitochondria, increase capillary density, and increase the mass and strength of connective tissue. The effects of age-related atrophy are especially pronounced in people who are sedentary, as the loss of muscle cells is displayed as functional impairments such as trouble with locomotion, balance, and posture. This can lead to a decrease in quality of life and medical problems, such as joint problems because the muscles that stabilize bones and joints are weakened. Problems with locomotion and balance can also cause various injuries due to falls.

Chapter Review

Hypertrophy is an increase in muscle mass due to the addition of structural proteins. The opposite of hypertrophy is atrophy, the loss of muscle mass due to the breakdown of structural proteins. Endurance exercise causes an increase in cellular mitochondria, myoglobin, and capillary networks in SO fibers. Endurance athletes have a high level of SO fibers relative to the other fiber types. Resistance exercise causes hypertrophy. Power-producing muscles have a higher number of FG fibers than of slow fibers. Strenuous exercise causes muscle cell damage that requires time to heal. Some athletes use performance-enhancing substances to enhance muscle performance. Muscle atrophy due to age is called sarcopenia and occurs as muscle fibers die and are replaced by connective and adipose tissue.

Review Questions

The muscles of a professional sprinter are most likely to have ______.

1. 80 percent fast-twitch muscle fibers and 20 percent slow-twitch muscle fibers
2. 20 percent fast-twitch muscle fibers and 80 percent slow-twitch muscle fibers

3. 50 percent fast-twitch muscle fibers and 50 percent slow-twitch muscle fibers
4. 40 percent fast-twitch muscle fibers and 60 percent slow-twitch muscle fibers

---

A

The muscles of a professional marathon runner are most likely to have _____.

1. 80 percent fast-twitch muscle fibers and 20 percent slow-twitch muscle fibers
2. 20 percent fast-twitch muscle fibers and 80 percent slow-twitch muscle fibers
3. 50 percent fast-twitch muscle fibers and 50 percent slow-twitch muscle fibers
4. 40 percent fast-twitch muscle fibers and 60 percent slow-twitch muscle fibers

---

B

Which of the following statements is *true*?

1. Fast fibers have a small diameter.
2. Fast fibers contain loosely packed myofibrils.
3. Fast fibers have large glycogen reserves.
4. Fast fibers have many mitochondria.

C

Which of the following statements is *false*?

1. Slow fibers have a small network of capillaries.
2. Slow fibers contain the pigment myoglobin.
3. Slow fibers contain a large number of mitochondria.
4. Slow fibers contract for extended periods.

A

Critical Thinking Questions

What changes occur at the cellular level in response to endurance training?

Endurance training modifies slow fibers to make them more efficient by producing more mitochondria to enable more aerobic metabolism and more ATP production. Endurance exercise can also increase the amount of myoglobin in a cell and formation of

more extensive capillary networks around the fiber.

What changes occur at the cellular level in response to resistance training?

Resistance exercises affect muscles by causing the formation of more actin and myosin, increasing the structure of muscle fibers.

Glossary

angiogenesis
: formation of blood capillary networks

atrophy
: loss of structural proteins from muscle fibers

hypertrophy
: addition of structural proteins to muscle fibers

sarcopenia
: age-related muscle atrophy

Cardiac Muscle Tissue

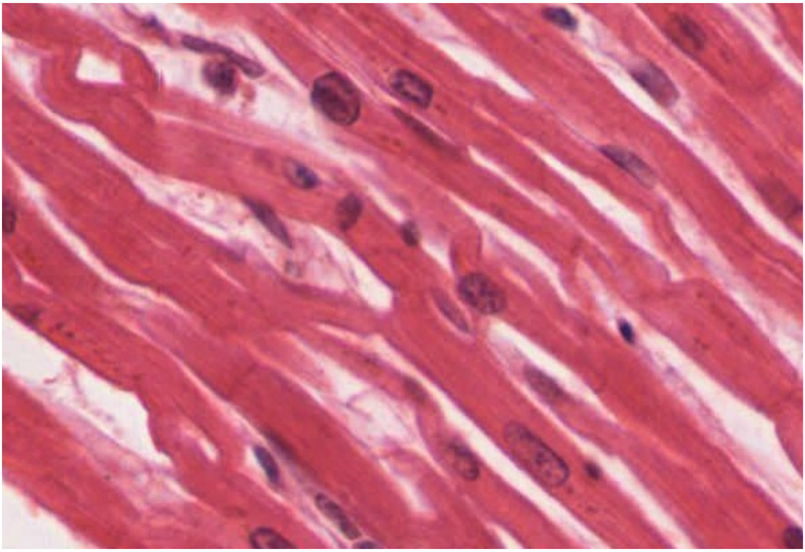
By the end of this section, you will be able to:

- Describe intercalated discs and gap junctions
- Describe a desmosome

Cardiac muscle tissue is only found in the heart. Highly coordinated contractions of cardiac muscle pump blood into the vessels of the circulatory system. Similar to skeletal muscle, cardiac muscle is striated and organized into sarcomeres, possessing the same banding organization as skeletal muscle ([link]). However, cardiac muscle fibers are shorter than skeletal muscle fibers and usually contain only one nucleus, which is located in the central region of the cell. Cardiac muscle fibers also possess many mitochondria and myoglobin, as ATP is produced primarily through aerobic metabolism. Cardiac muscle fibers cells also are extensively branched and are connected to one another at their ends by intercalated discs. An **intercalated disc** allows the cardiac muscle cells to contract in a wave-like pattern so that the heart can work as a pump.

Cardiac Muscle Tissue

Cardiac muscle tissue is only found in the heart. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



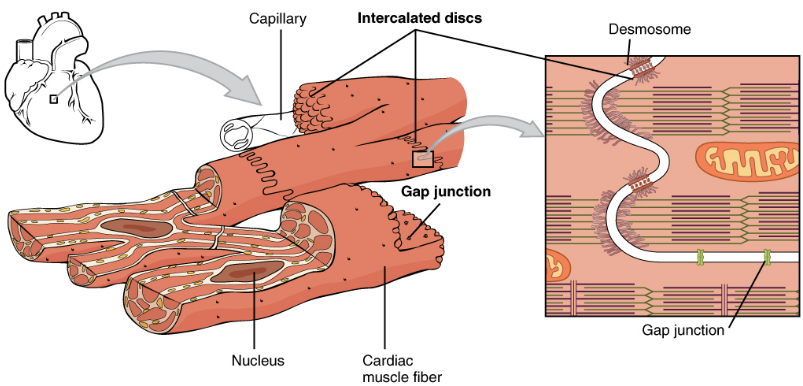
View the University of Michigan WebScope to explore the tissue sample in greater detail.

Intercalated discs are part of the sarcolemma and contain two structures important in cardiac muscle contraction: gap junctions and desmosomes. A gap

junction forms channels between adjacent cardiac muscle fibers that allow the depolarizing current produced by cations to flow from one cardiac muscle cell to the next. This joining is called electric coupling, and in cardiac muscle it allows the quick transmission of action potentials and the coordinated contraction of the entire heart. This network of electrically connected cardiac muscle cells creates a functional unit of contraction called a syncytium. The remainder of the intercalated disc is composed of desmosomes. A **desmosome** is a cell structure that anchors the ends of cardiac muscle fibers together so the cells do not pull apart during the stress of individual fibers contracting ([link]).

Cardiac Muscle

Intercalated discs are part of the cardiac muscle sarcolemma and they contain gap junctions and desmosomes.



Contractions of the heart (heartbeats) are controlled by specialized cardiac muscle cells called pacemaker cells that directly control heart rate. Although cardiac muscle cannot be consciously controlled, the

pacemaker cells respond to signals from the autonomic nervous system (ANS) to speed up or slow down the heart rate. The pacemaker cells can also respond to various hormones that modulate heart rate to control blood pressure.

The wave of contraction that allows the heart to work as a unit, called a functional syncytium, begins with the pacemaker cells. This group of cells is self-excitable and able to depolarize to threshold and fire action potentials on their own, a feature called **autorhythmicity**; they do this at set intervals which determine heart rate. Because they are connected with gap junctions to surrounding muscle fibers and the specialized fibers of the heart's conduction system, the pacemaker cells are able to transfer the depolarization to the other cardiac muscle fibers in a manner that allows the heart to contract in a coordinated manner.

Another feature of cardiac muscle is its relatively long action potentials in its fibers, having a sustained depolarization "plateau." The plateau is produced by Ca^{++} entry though voltage-gated calcium channels in the sarcolemma of cardiac muscle fibers. This sustained depolarization (and Ca^{++} entry) provides for a longer contraction than is produced by an action potential in skeletal muscle. Unlike skeletal muscle, a large percentage of the Ca^{++} that initiates contraction in cardiac muscles comes from outside the cell rather than from the SR.

Chapter Review

Cardiac muscle is striated muscle that is present only in the heart. Cardiac muscle fibers have a single nucleus, are branched, and joined to one another by intercalated discs that contain gap junctions for depolarization between cells and desmosomes to hold the fibers together when the heart contracts. Contraction in each cardiac muscle fiber is triggered by Ca^{++} ions in a similar manner as skeletal muscle, but here the Ca^{++} ions come from SR and through voltage-gated calcium channels in the sarcolemma. Pacemaker cells stimulate the spontaneous contraction of cardiac muscle as a functional unit, called a syncytium.

Review Questions

Cardiac muscles differ from skeletal muscles in that they ______.

1. are striated
2. utilize aerobic metabolism
3. contain myofibrils
4. contain intercalated discs

D

If cardiac muscle cells were prevented from undergoing aerobic metabolism, they ultimately would _____.

1. undergo glycolysis
2. synthesize ATP
3. stop contracting
4. start contracting

C

Critical Thinking Questions

What would be the drawback of cardiac contractions being the same duration as skeletal muscle contractions?

An action potential could reach a cardiac muscle cell before it has entered the relaxation phase, resulting in the sustained contractions of tetanus. If this happened, the heart would not beat regularly.

How are cardiac muscle cells similar to and different from skeletal muscle cells?

Cardiac and skeletal muscle cells both contain ordered myofibrils and are striated. Cardiac muscle cells are branched and contain intercalated discs, which skeletal muscles do not have.

Glossary

autorhythmicity
: heart’s ability to control its own contractions

desmosome
: cell structure that anchors the ends of cardiac muscle fibers to allow contraction to occur

intercalated disc
: part of the sarcolemma that connects cardiac tissue, and contains gap junctions and desmosomes

Smooth Muscle

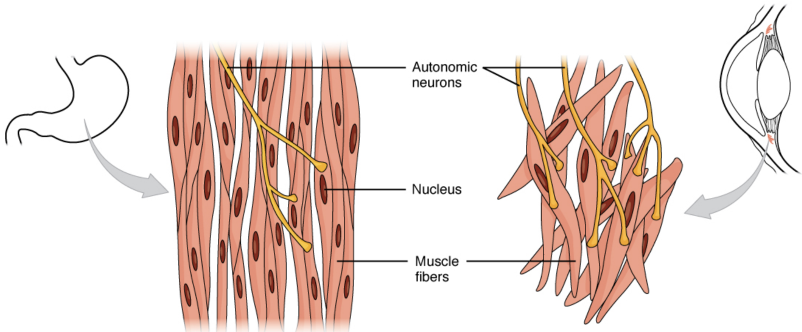
By the end of this section, you will be able to:

- Describe a dense body
- Explain how smooth muscle works with internal organs and passageways through the body
- Explain how smooth muscles differ from skeletal and cardiac muscles
- Explain the difference between single-unit and multi-unit smooth muscle

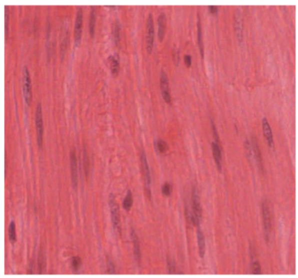
Smooth muscle (so-named because the cells do not have striations) is present in the walls of hollow organs like the urinary bladder, uterus, stomach, intestines, and in the walls of passageways, such as the arteries and veins of the circulatory system, and the tracts of the respiratory, urinary, and reproductive systems ([link]**ab**). Smooth muscle is also present in the eyes, where it functions to change the size of the iris and alter the shape of the lens; and in the skin where it causes hair to stand erect in response to cold temperature or fear.

Smooth Muscle Tissue

Smooth muscle tissue is found around organs in the digestive, respiratory, reproductive tracts and the iris of the eye. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



(a)



(b)

View the University of Michigan WebScope to explore the tissue sample in greater detail.

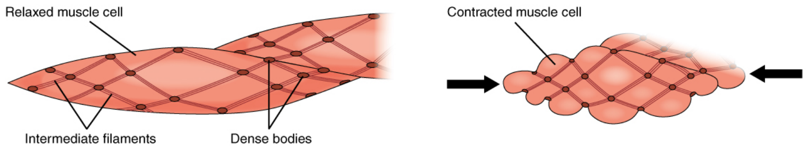
Smooth muscle fibers are spindle-shaped (wide in the middle and tapered at both ends, somewhat like a football) and have a single nucleus; they range from about 30 to 200 μm (thousands of times shorter than skeletal muscle fibers), and they produce their own connective tissue, endomysium. Although they do not have striations and sarcomeres, smooth muscle fibers do have actin and myosin contractile proteins, and thick and thin filaments. These thin filaments are anchored by dense bodies. A **dense body** is analogous to the Z-discs of skeletal and cardiac muscle fibers and is fastened to the sarcolemma. Calcium ions are supplied by the SR in the fibers and by sequestration from the extracellular fluid through membrane indentations called calveoli.

Because smooth muscle cells do not contain troponin, cross-bridge formation is not regulated by the troponin-tropomyosin complex but instead by the regulatory protein **calmodulin**. In a smooth muscle fiber, external Ca^{++} ions passing through opened calcium channels in the sarcolemma, and additional Ca^{++} released from SR, bind to calmodulin. The Ca^{++}-calmodulin complex then activates an enzyme called myosin (light chain) kinase, which, in turn, activates the myosin heads by phosphorylating them (converting ATP to ADP and P_i, with the P_i attaching to the head). The heads can then attach to actin-binding sites and pull on the thin filaments. The thin filaments also are

anchored to the dense bodies; the structures invested in the inner membrane of the sarcolemma (at adherens junctions) that also have cord-like intermediate filaments attached to them. When the thin filaments slide past the thick filaments, they pull on the dense bodies, structures tethered to the sarcolemma, which then pull on the intermediate filaments networks throughout the sarcoplasm. This arrangement causes the entire muscle fiber to contract in a manner whereby the ends are pulled toward the center, causing the midsection to bulge in a corkscrew motion ([link]).

Muscle Contraction

The dense bodies and intermediate filaments are networked through the sarcoplasm, which cause the muscle fiber to contract.



Although smooth muscle contraction relies on the presence of Ca^{++} ions, smooth muscle fibers have a much smaller diameter than skeletal muscle cells. T-tubules are not required to reach the interior of the cell and therefore not necessary to transmit an action potential deep into the fiber. Smooth muscle fibers have a limited calcium-storing SR but have calcium channels in the sarcolemma (similar to cardiac muscle fibers) that open during the action potential along the sarcolemma. The influx of extracellular Ca^{++} ions, which diffuse into the

sarcoplasm to reach the calmodulin, accounts for most of the Ca^{++} that triggers contraction of a smooth muscle cell.

Muscle contraction continues until ATP-dependent calcium pumps actively transport Ca^{++} ions back into the SR and out of the cell. However, a low concentration of calcium remains in the sarcoplasm to maintain muscle tone. This remaining calcium keeps the muscle slightly contracted, which is important in certain tracts and around blood vessels.

Because most smooth muscles must function for long periods without rest, their power output is relatively low, but contractions can continue without using large amounts of energy. Some smooth muscle can also maintain contractions even as Ca^{++} is removed and myosin kinase is inactivated/dephosphorylated. This can happen as a subset of cross-bridges between myosin heads and actin, called **latch-bridges**, keep the thick and thin filaments linked together for a prolonged period, and without the need for ATP. This allows for the maintaining of muscle “tone” in smooth muscle that lines arterioles and other visceral organs with very little energy expenditure.

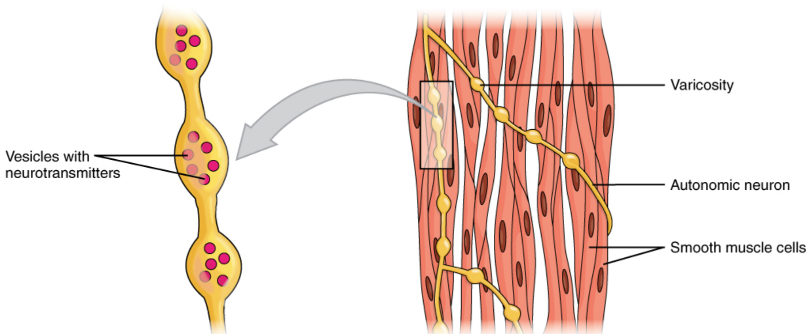
Smooth muscle is not under voluntary control; thus, it is called involuntary muscle. The triggers for smooth muscle contraction include hormones, neural stimulation by the ANS, and local factors. In

certain locations, such as the walls of visceral organs, stretching the muscle can trigger its contraction (the stress-relaxation response).

Axons of neurons in the ANS do not form the highly organized NMJs with smooth muscle, as seen between motor neurons and skeletal muscle fibers. Instead, there is a series of neurotransmitter-filled bulges called varicosities as an axon courses through smooth muscle, loosely forming motor units ([link]). A **varicosity** releases neurotransmitters into the synaptic cleft. Also, visceral muscle in the walls of the hollow organs (except the heart) contains pacesetter cells. A **pacesetter cell** can spontaneously trigger action potentials and contractions in the muscle.

Motor Units

A series of axon-like swelling, called varicosities or "boutons," from autonomic neurons form motor units through the smooth muscle.



Smooth muscle is organized in two ways: as single-unit smooth muscle, which is much more common; and as multiunit smooth muscle. The two types have

different locations in the body and have different characteristics. Single-unit muscle has its muscle fibers joined by gap junctions so that the muscle contracts as a single unit. This type of smooth muscle is found in the walls of all visceral organs except the heart (which has cardiac muscle in its walls), and so it is commonly called **visceral muscle**. Because the muscle fibers are not constrained by the organization and stretchability limits of sarcomeres, visceral smooth muscle has a **stress-relaxation response**. This means that as the muscle of a hollow organ is stretched when it fills, the mechanical stress of the stretching will trigger contraction, but this is immediately followed by relaxation so that the organ does not empty its contents prematurely. This is important for hollow organs, such as the stomach or urinary bladder, which continuously expand as they fill. The smooth muscle around these organs also can maintain a muscle tone when the organ empties and shrinks, a feature that prevents "flabbiness" in the empty organ. In general, visceral smooth muscle produces slow, steady contractions that allow substances, such as food in the digestive tract, to move through the body.

Multiunit smooth muscle cells rarely possess gap junctions, and thus are not electrically coupled. As a result, contraction does not spread from one cell to the next, but is instead confined to the cell that was originally stimulated. Stimuli for multiunit smooth

muscles come from autonomic nerves or hormones but not from stretching. This type of tissue is found around large blood vessels, in the respiratory airways, and in the eyes.

Hyperplasia in Smooth Muscle

Similar to skeletal and cardiac muscle cells, smooth muscle can undergo hypertrophy to increase in size. Unlike other muscle, smooth muscle can also divide to produce more cells, a process called **hyperplasia**. This can most evidently be observed in the uterus at puberty, which responds to increased estrogen levels by producing more uterine smooth muscle fibers, and greatly increases the size of the myometrium.

Sections Summary

Smooth muscle is found throughout the body around various organs and tracts. Smooth muscle cells have a single nucleus, and are spindle-shaped. Smooth muscle cells can undergo hyperplasia, mitotically dividing to produce new cells. The smooth cells are nonstriated, but their sarcoplasm is filled with actin and myosin, along with dense bodies in the sarcolemma to anchor the thin filaments and a network of intermediate filaments involved in pulling the sarcolemma toward the

fiber’s middle, shortening it in the process. Ca^{++} ions trigger contraction when they are released from SR and enter through opened voltage-gated calcium channels. Smooth muscle contraction is initiated when the Ca^{++} binds to intracellular calmodulin, which then activates an enzyme called myosin kinase that phosphorylates myosin heads so they can form the cross-bridges with actin and then pull on the thin filaments. Smooth muscle can be stimulated by pacesetter cells, by the autonomic nervous system, by hormones, spontaneously, or by stretching. The fibers in some smooth muscle have latch-bridges, cross-bridges that cycle slowly without the need for ATP; these muscles can maintain low-level contractions for long periods. Single-unit smooth muscle tissue contains gap junctions to synchronize membrane depolarization and contractions so that the muscle contracts as a single unit. Single-unit smooth muscle in the walls of the viscera, called visceral muscle, has a stress-relaxation response that permits muscle to stretch, contract, and relax as the organ expands. Multiunit smooth muscle cells do not possess gap junctions, and contraction does not spread from one cell to the next.

Multiple Choice

Smooth muscles differ from skeletal and cardiac muscles in that they ______.

1. lack myofibrils
2. are under voluntary control
3. lack myosin
4. lack actin

A

Which of the following statements describes smooth muscle cells?

1. They are resistant to fatigue.
2. They have a rapid onset of contractions.
3. They cannot exhibit tetanus.
4. They primarily use anaerobic metabolism.

A

Critical Thinking Questions

Why can smooth muscles contract over a wider range of resting lengths than skeletal and cardiac muscle?

Smooth muscles can contract over a wider range of resting lengths because the actin and myosin filaments in smooth muscle are not as rigidly organized as those in skeletal and cardiac muscle.

Describe the differences between single-unit smooth muscle and multiunit smooth muscle.

Single-unit smooth muscle is found in the walls of hollow organs; multiunit smooth muscle is found in airways to the lungs and large arteries. Single-unit smooth muscle cells contract synchronously, they are coupled by gap junctions, and they exhibit spontaneous action potential. Multiunit smooth cells lack gap junctions, and their contractions are not synchronous.

Glossary

calmodulin
: regulatory protein that facilitates contraction in smooth muscles

dense body
: sarcoplasmic structure that attaches to the sarcolemma and shortens the muscle as thin

filaments slide past thick filaments

hyperplasia
: process in which one cell splits to produce new cells

latch-bridges
: subset of a cross-bridge in which actin and myosin remain locked together

pacesetter cell
: cell that triggers action potentials in smooth muscle

stress-relaxation response
: relaxation of smooth muscle tissue after being stretched

varicosity
: enlargement of neurons that release neurotransmitters into synaptic clefts

visceral muscle
: smooth muscle found in the walls of visceral organs

Development and Regeneration of Muscle Tissue

By the end of this section, you will be able to:

- Describe the function of satellite cells
- Define fibrosis
- Explain which muscle has the greatest regeneration ability

Most muscle tissue of the body arises from embryonic mesoderm. Paraxial mesodermal cells adjacent to the neural tube form blocks of cells called **somites**. Skeletal muscles, excluding those of the head and limbs, develop from mesodermal somites, whereas skeletal muscle in the head and limbs develop from general mesoderm. Somites give rise to myoblasts. A **myoblast** is a muscle-forming stem cell that migrates to different regions in the body and then fuse(s) to form a syncytium, or **myotube**. As a myotube is formed from many different myoblast cells, it contains many nuclei, but has a continuous cytoplasm. This is why skeletal muscle cells are multinucleate, as the nucleus of each contributing myoblast remains intact in the mature skeletal muscle cell. However, cardiac and smooth muscle cells are not multinucleate because the myoblasts that form their cells do not fuse.

Gap junctions develop in the cardiac and single-unit smooth muscle in the early stages of development. In skeletal muscles, ACh receptors are initially present along most of the surface of the myoblasts,

but spinal nerve innervation causes the release of growth factors that stimulate the formation of motor end-plates and NMJs. As neurons become active, electrical signals that are sent through the muscle influence the distribution of slow and fast fibers in the muscle.

Although the number of muscle cells is set during development, satellite cells help to repair skeletal muscle cells. A **satellite cell** is similar to a myoblast because it is a type of stem cell; however, satellite cells are incorporated into muscle cells and facilitate the protein synthesis required for repair and growth. These cells are located outside the sarcolemma and are stimulated to grow and fuse with muscle cells by growth factors that are released by muscle fibers under certain forms of stress. Satellite cells can regenerate muscle fibers to a very limited extent, but they primarily help to repair damage in living cells. If a cell is damaged to a greater extent than can be repaired by satellite cells, the muscle fibers are replaced by scar tissue in a process called **fibrosis**. Because scar tissue cannot contract, muscle that has sustained significant damage loses strength and cannot produce the same amount of power or endurance as it could before being damaged.

Smooth muscle tissue can regenerate from a type of stem cell called a **pericyte**, which is found in some small blood vessels. Pericytes allow smooth muscle cells to regenerate and repair much more readily

than skeletal and cardiac muscle tissue. Similar to skeletal muscle tissue, cardiac muscle does not regenerate to a great extent. Dead cardiac muscle tissue is replaced by scar tissue, which cannot contract. As scar tissue accumulates, the heart loses its ability to pump because of the loss of contractile power. However, some minor regeneration may occur due to stem cells found in the blood that occasionally enter cardiac tissue.

Career Connections

Physical Therapist

As muscle cells die, they are not regenerated but instead are replaced by connective tissue and adipose tissue, which do not possess the contractile abilities of muscle tissue. Muscles atrophy when they are not used, and over time if atrophy is prolonged, muscle cells die. It is therefore important that those who are susceptible to muscle atrophy exercise to maintain muscle function and prevent the complete loss of muscle tissue. In extreme cases, when movement is not possible, electrical stimulation can be introduced to a muscle from an external source. This acts as a substitute for endogenous neural stimulation, stimulating the muscle to contract and preventing the loss of proteins that occurs with a lack of use. Physiotherapists work with patients to maintain muscles. They are trained to target muscles

susceptible to atrophy, and to prescribe and monitor exercises designed to stimulate those muscles. There are various causes of atrophy, including mechanical injury, disease, and age. After breaking a limb or undergoing surgery, muscle use is impaired and can lead to disuse atrophy. If the muscles are not exercised, this atrophy can lead to long-term muscle weakness. A stroke can also cause muscle impairment by interrupting neural stimulation to certain muscles. Without neural inputs, these muscles do not contract and thus begin to lose structural proteins. Exercising these muscles can help to restore muscle function and minimize functional impairments. Age-related muscle loss is also a target of physical therapy, as exercise can reduce the effects of age-related atrophy and improve muscle function.

The goal of a physiotherapist is to improve physical functioning and reduce functional impairments; this is achieved by understanding the cause of muscle impairment and assessing the capabilities of a patient, after which a program to enhance these capabilities is designed. Some factors that are assessed include strength, balance, and endurance, which are continually monitored as exercises are introduced to track improvements in muscle function. Physiotherapists can also instruct patients on the proper use of equipment, such as crutches, and assess whether someone has sufficient strength to use the equipment and when they can function without it.

Chapter Review

Muscle tissue arises from embryonic mesoderm. Somites give rise to myoblasts and fuse to form a myotube. The nucleus of each contributing myoblast remains intact in the mature skeletal muscle cell, resulting in a mature, multinucleate cell. Satellite cells help to repair skeletal muscle cells. Smooth muscle tissue can regenerate from stem cells called pericytes, whereas dead cardiac muscle tissue is replaced by scar tissue. Aging causes muscle mass to decrease and be replaced by noncontractile connective tissue and adipose tissue.

Review Questions

From which embryonic cell type does muscle tissue develop?

1. ganglion cells
2. myotube cells
3. myoblast cells
4. satellite cells

C

Which cell type helps to repair injured muscle fibers?

1. ganglion cells
2. myotube cells
3. myoblast cells
4. satellite cells

D

Critical Thinking Questions

Why is muscle that has sustained significant damage unable to produce the same amount of power as it could before being damaged?

If the damage exceeds what can be repaired by satellite cells, the damaged tissue is replaced by scar tissue, which cannot contract.

Which muscle type(s) (skeletal, smooth, or cardiac) can regenerate new muscle cells/fibers? Explain your answer.

Smooth muscle tissue can regenerate from stem

cells called pericytes, cells found in some small blood vessels. These allow smooth muscle cells to regenerate and repair much more readily than skeletal and cardiac muscle tissue.

Glossary

fibrosis
: replacement of muscle fibers by scar tissue

myoblast
: muscle-forming stem cell

myotube
: fusion of many myoblast cells

pericyte
: stem cell that regenerates smooth muscle cells

satellite cell
: stem cell that helps to repair muscle cells

somites
: blocks of paraxial mesoderm cells

Introduction
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Robotic Arms Playing Foosball
As the neural circuitry of the nervous system has become more fully understood and robotics more sophisticated, it is now possible to integrate technology with the body and restore abilities following traumatic events. At some point in the future, will this type of technology lead to the ability to augment our nervous systems? (credit: U.S. Army/Wikimedia Commons)

Chapter Objectives

After studying this chapter, you will be able to:

- Name the major divisions of the nervous system, both anatomical and functional
- Describe the functional and structural differences between gray matter and white matter structures
- Name the parts of the multipolar neuron in order of polarity
- List the types of glial cells and assign each to the proper division of the nervous system, along with their function(s)
- Distinguish the major functions of the nervous system: sensation, integration, and response
- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential
- Explain the differences between types of graded potentials
- Categorize the major neurotransmitters by chemical type and effect

The nervous system is a very complex organ system. In Peter D. Kramer's book *Listening to Prozac*, a pharmaceutical researcher is quoted as saying, "If the human brain were simple enough for us to understand, we would be too simple to understand it" (1994). That quote is from the early 1990s; in the two decades since, progress has continued at an amazing rate within the scientific disciplines of

neuroscience. It is an interesting conundrum to consider that the complexity of the nervous system may be too complex for it (that is, for us) to completely unravel. But our current level of understanding is probably nowhere close to that limit.

One easy way to begin to understand the structure of the nervous system is to start with the large divisions and work through to a more in-depth understanding. In other chapters, the finer details of the nervous system will be explained, but first looking at an overview of the system will allow you to begin to understand how its parts work together. The focus of this chapter is on nervous (neural) tissue, both its structure and its function. But before you learn about that, you will see a big picture of the system—actually, a few big pictures.

Basic Structure and Function of the Nervous System

By the end of this section, you will be able to:

- Identify the anatomical and functional divisions of the nervous system
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons
- List the basic functions of the nervous system

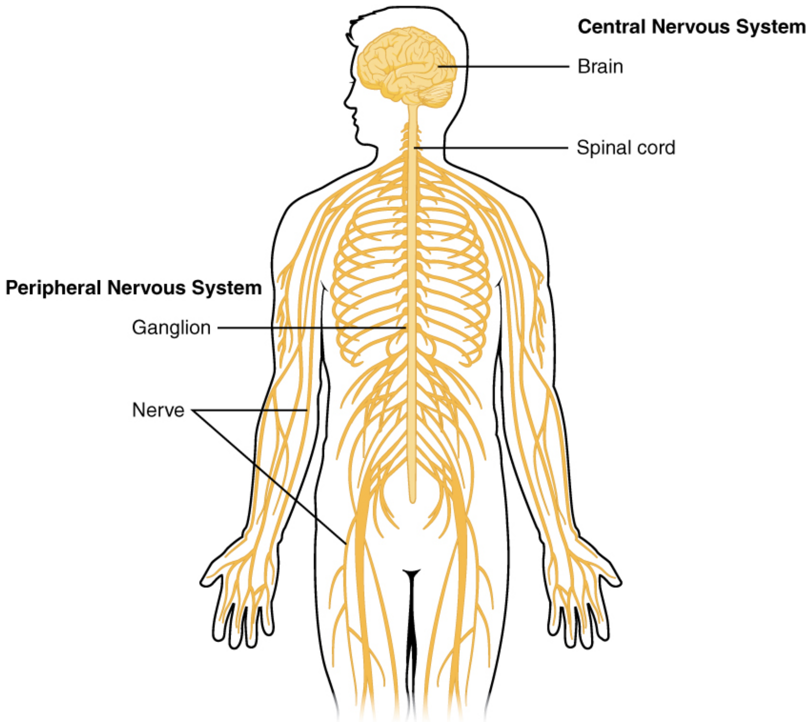
The picture you have in your mind of the nervous system probably includes the **brain**, the nervous tissue contained within the cranium, and the **spinal cord**, the extension of nervous tissue within the vertebral column. That suggests it is made of two organs—and you may not even think of the spinal cord as an organ—but the nervous system is a very complex structure. Within the brain, many different and separate regions are responsible for many different and separate functions. It is as if the nervous system is composed of many organs that all look similar and can only be differentiated using tools such as the microscope or electrophysiology. In comparison, it is easy to see that the stomach is different than the esophagus or the liver, so you can imagine the digestive system as a collection of specific organs.

The Central and Peripheral Nervous Systems

The nervous system can be divided into two major regions: the central and peripheral nervous systems. The **central nervous system (CNS)** is the brain and spinal cord, and the **peripheral nervous system (PNS)** is everything else ([link]). The brain is contained within the cranial cavity of the skull, and the spinal cord is contained within the vertebral cavity of the vertebral column. It is a bit of an oversimplification to say that the CNS is what is inside these two cavities and the peripheral nervous system is outside of them, but that is one way to start to think about it. In actuality, there are some elements of the peripheral nervous system that are within the cranial or vertebral cavities. The peripheral nervous system is so named because it is on the periphery—meaning beyond the brain and spinal cord. Depending on different aspects of the nervous system, the dividing line between central and peripheral is not necessarily universal.

Central and Peripheral Nervous System

The structures of the PNS are referred to as ganglia and nerves, which can be seen as distinct structures. The equivalent structures in the CNS are not obvious from this overall perspective and are best examined in prepared tissue under the microscope.



Nervous tissue, present in both the CNS and PNS, contains two basic types of cells: neurons and glial cells. A **glial cell** is one of a variety of cells that provide a framework of tissue that supports the neurons and their activities. The **neuron** is the more functionally important of the two, in terms of the communicative function of the nervous system. To describe the functional divisions of the nervous system, it is important to understand the structure of a neuron. Neurons are cells and therefore have a **soma**, or cell body, but they also have extensions of the cell; each extension is generally referred to as a **process**. There is one important process that every neuron has called an **axon**, which is the fiber that

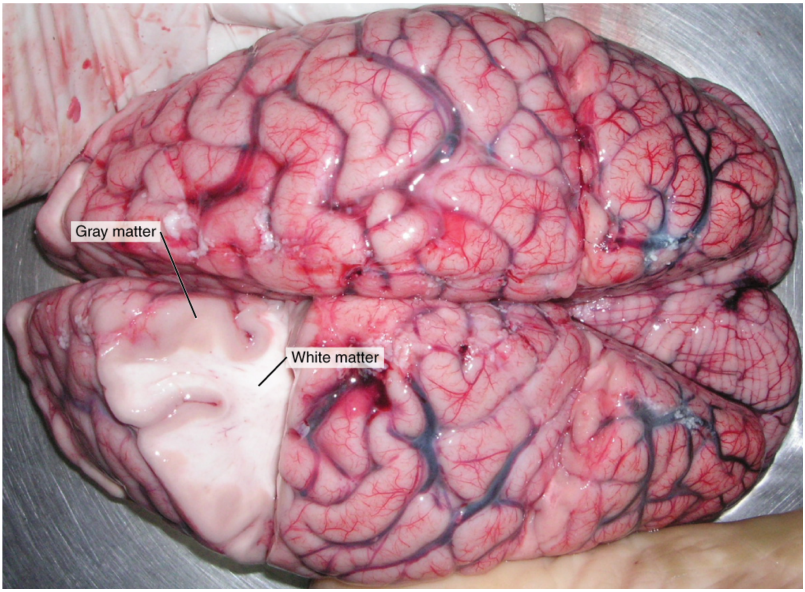
connects a neuron with its target. Another type of process that branches off from the soma is the **dendrite**. Dendrites are responsible for receiving most of the input from other neurons. Looking at nervous tissue, there are regions that predominantly contain cell bodies and regions that are largely composed of just axons. These two regions within nervous system structures are often referred to as **gray matter** (the regions with many cell bodies and dendrites) or **white matter** (the regions with many axons). [link] demonstrates the appearance of these regions in the brain and spinal cord. The colors ascribed to these regions are what would be seen in "fresh," or unstained, nervous tissue. Gray matter is not necessarily gray. It can be pinkish because of blood content, or even slightly tan, depending on how long the tissue has been preserved. But white matter is white because axons are insulated by a lipid-rich substance called **myelin**. Lipids can appear as white ("fatty") material, much like the fat on a raw piece of chicken or beef. Actually, gray matter may have that color ascribed to it because next to the white matter, it is just darker—hence, gray.

The distinction between gray matter and white matter is most often applied to central nervous tissue, which has large regions that can be seen with the unaided eye. When looking at peripheral structures, often a microscope is used and the tissue is stained with artificial colors. That is not to say

that central nervous tissue cannot be stained and viewed under a microscope, but unstained tissue is most likely from the CNS—for example, a frontal section of the brain or cross section of the spinal cord.

Gray Matter and White Matter

A brain removed during an autopsy, with a partial section removed, shows white matter surrounded by gray matter. Gray matter makes up the outer cortex of the brain. (credit: modification of work by "Suseno"/Wikimedia Commons)

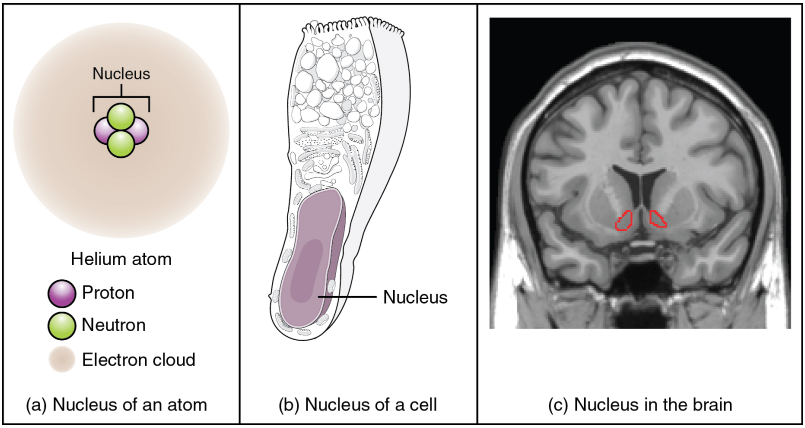


Regardless of the appearance of stained or unstained tissue, the cell bodies of neurons or axons can be located in discrete anatomical structures that need to be named. Those names are specific to whether the structure is central or peripheral. A localized collection of neuron cell bodies in the CNS is

referred to as a **nucleus**. In the PNS, a cluster of neuron cell bodies is referred to as a **ganglion**. [link] indicates how the term nucleus has a few different meanings within anatomy and physiology. It is the center of an atom, where protons and neutrons are found; it is the center of a cell, where the DNA is found; and it is a center of some function in the CNS. There is also a potentially confusing use of the word ganglion (plural = ganglia) that has a historical explanation. In the central nervous system, there is a group of nuclei that are connected together and were once called the basal ganglia before "ganglion" became accepted as a description for a peripheral structure. Some sources refer to this group of nuclei as the "basal nuclei" to avoid confusion.

What Is a Nucleus?

(a) The nucleus of an atom contains its protons and neutrons. (b) The nucleus of a cell is the organelle that contains DNA. (c) A nucleus in the CNS is a localized center of function with the cell bodies of several neurons, shown here circled in red. (credit c: "Was a bee"/Wikimedia Commons)

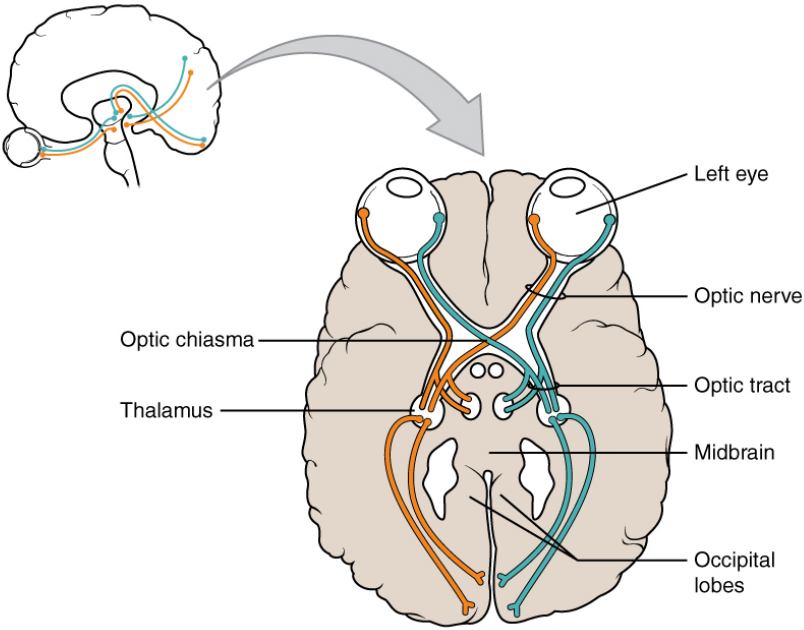


Terminology applied to bundles of axons also differs depending on location. A bundle of axons, or fibers, found in the CNS is called a **tract** whereas the same thing in the PNS would be called a **nerve**. There is an important point to make about these terms, which is that they can both be used to refer to the same bundle of axons. When those axons are in the PNS, the term is nerve, but if they are CNS, the term is tract. The most obvious example of this is the axons that project from the retina into the brain. Those axons are called the optic nerve as they leave the eye, but when they are inside the cranium, they are referred to as the optic tract. There is a specific place where the name changes, which is the optic chiasm, but they are still the same axons ([link]). A similar situation outside of science can be described for some roads. Imagine a road called “Broad Street” in a town called “Anyville.” The road leaves Anyville and goes to the next town over, called “Hometown.” When the road crosses the line between the two towns and is in Hometown, its

name changes to “Main Street.” That is the idea behind the naming of the retinal axons. In the PNS, they are called the optic nerve, and in the CNS, they are the optic tract. [link] helps to clarify which of these terms apply to the central or peripheral nervous systems.

Optic Nerve Versus Optic Tract

This drawing of the connections of the eye to the brain shows the optic nerve extending from the eye to the chiasm, where the structure continues as the optic tract. The same axons extend from the eye to the brain through these two bundles of fibers, but the chiasm represents the border between peripheral and central.



In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize web site to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from X-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

Structures of the CNS and PNS	CNS	PNS
Group of Neuron Cell Bodies (i.e., gray matter)	Nucleus	Ganglion
Bundle of Axons (i.e., white matter)	Tract	Nerve

Functional Divisions of the Nervous System

The nervous system can also be divided on the basis of its functions, but anatomical divisions and functional divisions are different. The CNS and the PNS both contribute to the same functions, but those functions can be attributed to different regions of the brain (such as the cerebral cortex or the hypothalamus) or to different ganglia in the periphery. The problem with trying to fit functional differences into anatomical divisions is that sometimes the same structure can be part of several functions. For example, the optic nerve carries signals from the retina that are either used for the conscious perception of visual stimuli, which takes place in the cerebral cortex, or for the reflexive

responses of smooth muscle tissue that are processed through the hypothalamus.

There are two ways to consider how the nervous system is divided functionally. First, the basic functions of the nervous system are sensation, integration, and response. Secondly, control of the body can be somatic or autonomic—divisions that are largely defined by the structures that are involved in the response. There is also a region of the peripheral nervous system that is called the enteric nervous system that is responsible for a specific set of the functions within the realm of autonomic control related to gastrointestinal functions.

Basic Functions

The nervous system is involved in receiving information about the environment around us (sensation) and generating responses to that information (motor responses). The nervous system can be divided into regions that are responsible for **sensation** (sensory functions) and for the **response** (motor functions). But there is a third function that needs to be included. Sensory input needs to be integrated with other sensations, as well as with memories, emotional state, or learning (cognition). Some regions of the nervous system are termed **integration** or association areas. The process of integration combines sensory perceptions and

higher cognitive functions such as memories, learning, and emotion to produce a response.

Sensation. The first major function of the nervous system is sensation—receiving information about the environment to gain input about what is happening outside the body (or, sometimes, within the body). The sensory functions of the nervous system register the presence of a change from homeostasis or a particular event in the environment, known as a **stimulus**. The senses we think of most are the "big five": taste, smell, touch, sight, and hearing. The stimuli for taste and smell are both chemical substances (molecules, compounds, ions, etc.), touch is physical or mechanical stimuli that interact with the skin, sight is light stimuli, and hearing is the perception of sound, which is a physical stimulus similar to some aspects of touch. There are actually more senses than just those, but that list represents the major senses. Those five are all senses that receive stimuli from the outside world, and of which there is conscious perception. Additional sensory stimuli might be from the internal environment (inside the body), such as the stretch of an organ wall or the concentration of certain ions in the blood.

Response. The nervous system produces a response on the basis of the stimuli perceived by sensory structures. An obvious response would be the movement of muscles, such as withdrawing a hand

from a hot stove, but there are broader uses of the term. The nervous system can cause the contraction of all three types of muscle tissue. For example, skeletal muscle contracts to move the skeleton, cardiac muscle is influenced as heart rate increases during exercise, and smooth muscle contracts as the digestive system moves food along the digestive tract. Responses also include the neural control of glands in the body as well, such as the production and secretion of sweat by the eccrine and merocrine sweat glands found in the skin to lower body temperature.

Responses can be divided into those that are voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands). Voluntary responses are governed by the somatic nervous system and involuntary responses are governed by the autonomic nervous system, which are discussed in the next section.

Integration. Stimuli that are received by sensory structures are communicated to the nervous system where that information is processed. This is called integration. Stimuli are compared with, or integrated with, other stimuli, memories of previous stimuli, or the state of a person at a particular time. This leads to the specific response that will be generated. Seeing a baseball pitched to a batter will

not automatically cause the batter to swing. The trajectory of the ball and its speed will need to be considered. Maybe the count is three balls and one strike, and the batter wants to let this pitch go by in the hope of getting a walk to first base. Or maybe the batter's team is so far ahead, it would be fun to just swing away.

Controlling the Body

The nervous system can be divided into two parts mostly on the basis of a functional difference in responses. The **somatic nervous system (SNS)** is responsible for conscious perception and voluntary motor responses. Voluntary motor response means the contraction of skeletal muscle, but those contractions are not always voluntary in the sense that you have to want to perform them. Some somatic motor responses are reflexes, and often happen without a conscious decision to perform them. If your friend jumps out from behind a corner and yells "Boo!" you will be startled and you might scream or leap back. You didn't decide to do that, and you may not have wanted to give your friend a reason to laugh at your expense, but it is a reflex involving skeletal muscle contractions. Other motor responses become automatic (in other words, unconscious) as a person learns motor skills (referred to as "habit learning" or "procedural memory").

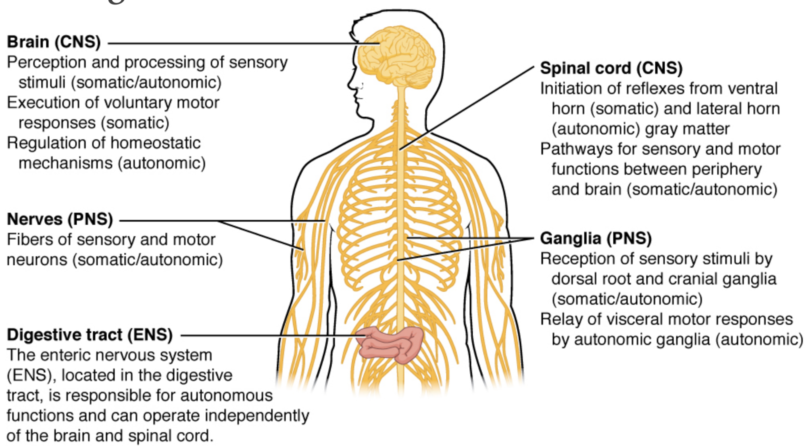
The **autonomic nervous system (ANS)** is responsible for involuntary control of the body, usually for the sake of homeostasis (regulation of the internal environment). Sensory input for autonomic functions can be from sensory structures tuned to external or internal environmental stimuli. The motor output extends to smooth and cardiac muscle as well as glandular tissue. The role of the autonomic system is to regulate the organ systems of the body, which usually means to control homeostasis. Sweat glands, for example, are controlled by the autonomic system. When you are hot, sweating helps cool your body down. That is a homeostatic mechanism. But when you are nervous, you might start sweating also. That is not homeostatic, it is the physiological response to an emotional state.

There is another division of the nervous system that describes functional responses. The **enteric nervous system (ENS)** is responsible for controlling the smooth muscle and glandular tissue in your digestive system. It is a large part of the PNS, and is not dependent on the CNS. It is sometimes valid, however, to consider the enteric system to be a part of the autonomic system because the neural structures that make up the enteric system are a component of the autonomic output that regulates digestion. There are some differences between the two, but for our purposes here there will be a good bit of overlap. See [link] for examples of where

these divisions of the nervous system can be found.

Somatic, Autonomic, and Enteric Structures of the Nervous System

Somatic structures include the spinal nerves, both motor and sensory fibers, as well as the sensory ganglia (posterior root ganglia and cranial nerve ganglia). Autonomic structures are found in the nerves also, but include the sympathetic and parasympathetic ganglia. The enteric nervous system includes the nervous tissue within the organs of the digestive tract.



Visit this site to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

Everyday Connection

How Much of Your Brain Do You Use?

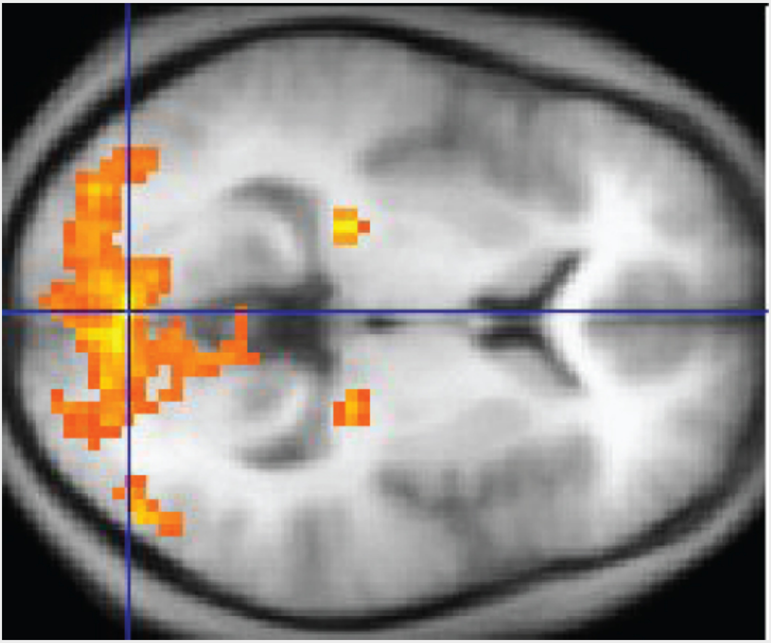
Have you ever heard the claim that humans only use 10 percent of their brains? Maybe you have seen an advertisement on a website saying that there is a secret to unlocking the full potential of your mind—as if there were 90 percent of your brain sitting idle, just waiting for you to use it. If you see an ad like that, don't click. It isn't true.

An easy way to see how much of the brain a person uses is to take measurements of brain activity while performing a task. An example of this kind of measurement is functional magnetic resonance imaging (fMRI), which generates a map of the most active areas and can be generated and presented in three dimensions ([link]). This procedure is different from the standard MRI technique because it is measuring changes in the tissue in time with

an experimental condition or event.

fMRI

This fMRI shows activation of the visual cortex in response to visual stimuli. (credit: “Superborsuk”/ Wikimedia Commons)



The underlying assumption is that active nervous tissue will have greater blood flow. By having the subject perform a visual task, activity all over the brain can be measured. Consider this possible experiment: the subject is told to look at a screen with a black dot in the middle (a fixation point). A photograph of a face is projected on the screen away from the center. The subject has to look at the photograph and decipher what it is. The subject has been instructed to push a button if the photograph is of someone they recognize. The photograph might be of a celebrity, so the subject

would press the button, or it might be of a random person unknown to the subject, so the subject would not press the button.

In this task, visual sensory areas would be active, integrating areas would be active, motor areas responsible for moving the eyes would be active, and motor areas for pressing the button with a finger would be active. Those areas are distributed all around the brain and the fMRI images would show activity in more than just 10 percent of the brain (some evidence suggests that about 80 percent of the brain is using energy—based on blood flow to the tissue—during well-defined tasks similar to the one suggested above). This task does not even include all of the functions the brain performs. There is no language response, the body is mostly lying still in the MRI machine, and it does not consider the autonomic functions that would be ongoing in the background.

Chapter Review

The nervous system can be separated into divisions on the basis of anatomy and physiology. The anatomical divisions are the central and peripheral nervous systems. The CNS is the brain and spinal cord. The PNS is everything else. Functionally, the

nervous system can be divided into those regions that are responsible for sensation, those that are responsible for integration, and those that are responsible for generating responses. All of these functional areas are found in both the central and peripheral anatomy.

Considering the anatomical regions of the nervous system, there are specific names for the structures within each division. A localized collection of neuron cell bodies is referred to as a nucleus in the CNS and as a ganglion in the PNS. A bundle of axons is referred to as a tract in the CNS and as a nerve in the PNS. Whereas nuclei and ganglia are specifically in the central or peripheral divisions, axons can cross the boundary between the two. A single axon can be part of a nerve and a tract. The name for that specific structure depends on its location.

Nervous tissue can also be described as gray matter and white matter on the basis of its appearance in unstained tissue. These descriptions are more often used in the CNS. Gray matter is where nuclei are found and white matter is where tracts are found. In the PNS, ganglia are basically gray matter and nerves are white matter.

The nervous system can also be divided on the basis of how it controls the body. The somatic nervous system (SNS) is responsible for functions that result

in moving skeletal muscles. Any sensory or integrative functions that result in the movement of skeletal muscle would be considered somatic. The autonomic nervous system (ANS) is responsible for functions that affect cardiac or smooth muscle tissue, or that cause glands to produce their secretions. Autonomic functions are distributed between central and peripheral regions of the nervous system. The sensations that lead to autonomic functions can be the same sensations that are part of initiating somatic responses. Somatic and autonomic integrative functions may overlap as well.

A special division of the nervous system is the enteric nervous system, which is responsible for controlling the digestive organs. Parts of the autonomic nervous system overlap with the enteric nervous system. The enteric nervous system is exclusively found in the periphery because it is the nervous tissue in the organs of the digestive system.

Interactive Link Questions

In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a

tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize website to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from x-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

MRI uses the relative amount of water in tissue to distinguish different areas, so gray and white matter in the nervous system can be seen clearly in these images.

Visit this site to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated

deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

They are part of the somatic nervous system, which is responsible for voluntary movements such as walking or climbing the stairs.

Review Questions

Which of the following cavities contains a component of the central nervous system?

1. abdominal
2. pelvic
3. cranial
4. thoracic

C

Which structure predominates in the white matter of the brain?

1. myelinated axons
2. neuronal cell bodies
3. ganglia of the parasympathetic nerves
4. bundles of dendrites from the enteric nervous system

A

Which part of a neuron transmits an electrical signal to a target cell?

1. dendrites
2. soma
3. cell body
4. axon

D

Which term describes a bundle of axons in the peripheral nervous system?

1. nucleus
2. ganglion
3. tract
4. nerve

D

Which functional division of the nervous system would be responsible for the physiological changes seen during exercise (e.g., increased heart rate and sweating)?

1. somatic
2. autonomic
3. enteric
4. central

B

Critical Thinking Questions

What responses are generated by the nervous system when you run on a treadmill? Include an example of each type of tissue that is under nervous system control.

Running on a treadmill involves contraction of the skeletal muscles in the legs, increase in contraction of the cardiac muscle of the heart, and the production and secretion of sweat in the skin to stay cool.

When eating food, what anatomical and functional divisions of the nervous system are involved in the perceptual experience?

The sensation of taste associated with eating is sensed by nerves in the periphery that are involved in sensory and somatic functions.

References

Kramer, PD. Listening to prozac. 1st ed. New York (NY): Penguin Books; 1993.

Glossary

autonomic nervous system (ANS)
: functional division of the nervous system that is responsible for homeostatic reflexes that coordinate control of cardiac and smooth muscle, as well as glandular tissue

axon
: single process of the neuron that carries an electrical signal (action potential) away from the cell body toward a target cell

brain
: the large organ of the central nervous system

composed of white and gray matter, contained within the cranium and continuous with the spinal cord

central nervous system (CNS)
: anatomical division of the nervous system located within the cranial and vertebral cavities, namely the brain and spinal cord

dendrite
: one of many branchlike processes that extends from the neuron cell body and functions as a contact for incoming signals (synapses) from other neurons or sensory cells

enteric nervous system (ENS)
: neural tissue associated with the digestive system that is responsible for nervous control through autonomic connections

ganglion
: localized collection of neuron cell bodies in the peripheral nervous system

glial cell
: one of the various types of neural tissue cells responsible for maintenance of the tissue, and largely responsible for supporting neurons

gray matter
: regions of the nervous system containing cell bodies of neurons with few or no myelinated

axons; actually may be more pink or tan in color, but called gray in contrast to white matter

integration
: nervous system function that combines sensory perceptions and higher cognitive functions (memories, learning, emotion, etc.) to produce a response

myelin
: lipid-rich insulating substance surrounding the axons of many neurons, allowing for faster transmission of electrical signals

nerve
: cord-like bundle of axons located in the peripheral nervous system that transmits sensory input and response output to and from the central nervous system

neuron
: neural tissue cell that is primarily responsible for generating and propagating electrical signals into, within, and out of the nervous system

nucleus
: in the nervous system, a localized collection of neuron cell bodies that are functionally related; a "center" of neural function

peripheral nervous system (PNS)
: anatomical division of the nervous system that is largely outside the cranial and vertebral cavities, namely all parts except the brain and spinal cord

process
: in cells, an extension of a cell body; in the case of neurons, this includes the axon and dendrites

response
: nervous system function that causes a target tissue (muscle or gland) to produce an event as a consequence to stimuli

sensation
: nervous system function that receives information from the environment and translates it into the electrical signals of nervous tissue

soma
: in neurons, that portion of the cell that contains the nucleus; the cell body, as opposed to the cell processes (axons and dendrites)

somatic nervous system (SNS)
: functional division of the nervous system that is concerned with conscious perception, voluntary movement, and skeletal muscle

reflexes

spinal cord
organ of the central nervous system found within the vertebral cavity and connected with the periphery through spinal nerves; mediates reflex behaviors

stimulus
an event in the external or internal environment that registers as activity in a sensory neuron

tract
bundle of axons in the central nervous system having the same function and point of origin

white matter
regions of the nervous system containing mostly myelinated axons, making the tissue appear white because of the high lipid content of myelin

Nervous Tissue
By the end of this section, you will be able to:

- Describe the basic structure of a neuron
- Identify the different types of neurons on the basis of polarity
- List the glial cells of the CNS and describe their function
- List the glial cells of the PNS and describe their function

Nervous tissue is composed of two types of cells, neurons and glial cells. Neurons are the primary type of cell that most anyone associates with the nervous system. They are responsible for the computation and communication that the nervous system provides. They are electrically active and release chemical signals to target cells. Glial cells, or glia, are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

Neurons

Neurons are the cells considered to be the basis of

nervous tissue. They are responsible for the electrical signals that communicate information about sensations, and that produce movements in response to those stimuli, along with inducing thought processes within the brain. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible.

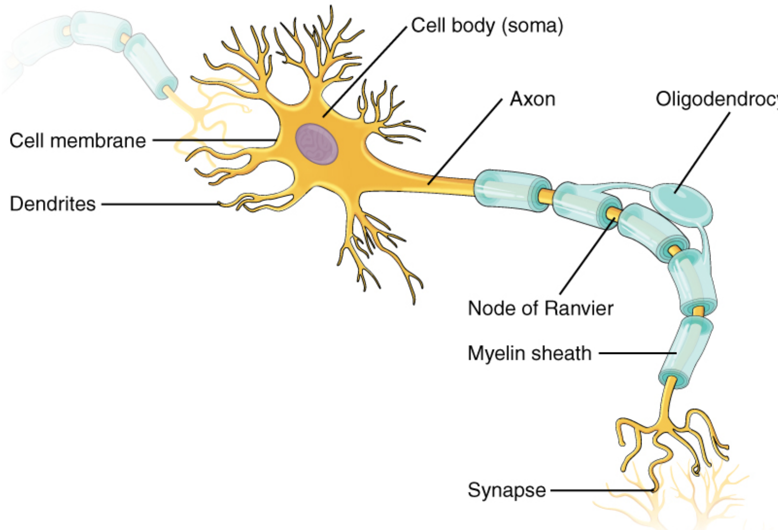
Parts of a Neuron

As you learned in the first section, the main part of a neuron is the cell body, which is also known as the soma (soma = “body”). The cell body contains the nucleus and most of the major organelles. But what makes neurons special is that they have many extensions of their cell membranes, which are generally referred to as processes. Neurons are usually described as having one, and only one, axon—a fiber that emerges from the cell body and projects to target cells. That single axon can branch repeatedly to communicate with many target cells. It is the axon that propagates the nerve impulse, which is communicated to one or more cells. The other processes of the neuron are dendrites, which receive information from other neurons at specialized areas of contact called **synapses**. The dendrites are usually highly branched processes, providing locations for other neurons to communicate with the cell body. Information flows

through a neuron from the dendrites, across the cell body, and down the axon. This gives the neuron a polarity—meaning that information flows in this one direction. [link] shows the relationship of these parts to one another.

Parts of a Neuron

The major parts of the neuron are labeled on a multipolar neuron from the CNS.



Where the axon emerges from the cell body, there is a special region referred to as the **axon hillock**. This is a tapering of the cell body toward the axon fiber. Within the axon hillock, the cytoplasm changes to a solution of limited components called **axoplasm**. Because the axon hillock represents the beginning of the axon, it is also referred to as the **initial segment**.

Many axons are wrapped by an insulating substance

called myelin, which is actually made from glial cells. Myelin acts as insulation much like the plastic or rubber that is used to insulate electrical wires. A key difference between myelin and the insulation on a wire is that there are gaps in the myelin covering of an axon. Each gap is called a **node of Ranvier** and is important to the way that electrical signals travel down the axon. The length of the axon between each gap, which is wrapped in myelin, is referred to as an **axon segment**. At the end of the axon is the **axon terminal**, where there are usually several branches extending toward the target cell, each of which ends in an enlargement called a **synaptic end bulb**. These bulbs are what make the connection with the target cell at the synapse.

Visit this site to learn about how nervous tissue is composed of neurons and glial cells. Neurons are dynamic cells with the ability to make a vast number of connections, to respond incredibly quickly to stimuli, and to initiate movements on

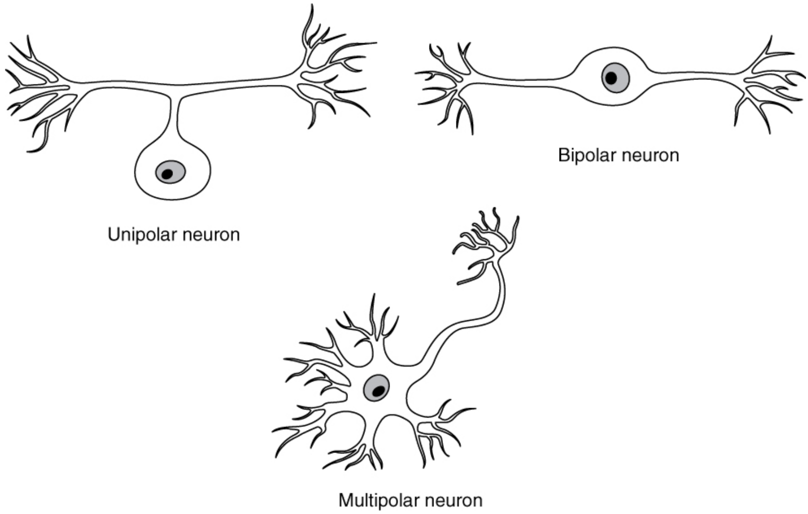
the basis of those stimuli. They are the focus of intense research because failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Based on what this article says about neuron function, why wouldn't they be helpful for plants or microorganisms?

Types of Neurons

There are many neurons in the nervous system—a number in the trillions. And there are many different types of neurons. They can be classified by many different criteria. The first way to classify them is by the number of processes attached to the cell body. Using the standard model of neurons, one of these processes is the axon, and the rest are dendrites. Because information flows through the neuron from dendrites or cell bodies toward the axon, these names are based on the neuron's polarity ([link]).

Neuron Classification by Shape

Unipolar cells have one process that includes both the axon and dendrite. Bipolar cells have two processes, the axon and a dendrite. Multipolar cells have more than two processes, the axon and two or more dendrites.



Unipolar cells have only one process emerging from the cell. True unipolar cells are only found in invertebrate animals, so the unipolar cells in humans are more appropriately called “pseudo-unipolar” cells. Invertebrate unipolar cells do not have dendrites. Human unipolar cells have an axon that emerges from the cell body, but it splits so that the axon can extend along a very long distance. At one end of the axon are dendrites, and at the other end, the axon forms synaptic connections with a target. Unipolar cells are exclusively sensory neurons and have two unique characteristics. First, their dendrites are receiving sensory information, sometimes directly from the stimulus itself. Secondly, the cell bodies of unipolar neurons are always found in ganglia. Sensory reception is a peripheral function (those dendrites are in the periphery, perhaps in the skin) so the cell body is in the periphery, though closer to the CNS in a

ganglion. The axon projects from the dendrite endings, past the cell body in a ganglion, and into the central nervous system.

Bipolar cells have two processes, which extend from each end of the cell body, opposite to each other. One is the axon and one the dendrite. Bipolar cells are not very common. They are found mainly in the olfactory epithelium (where smell stimuli are sensed), and as part of the retina.

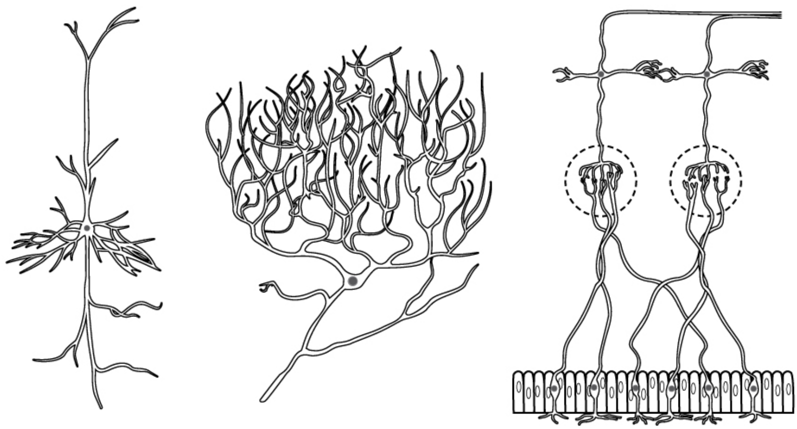
Multipolar neurons are all of the neurons that are not unipolar or bipolar. They have one axon and two or more dendrites (usually many more). With the exception of the unipolar sensory ganglion cells, and the two specific bipolar cells mentioned above, all other neurons are multipolar. Some cutting edge research suggests that certain neurons in the CNS do not conform to the standard model of "one, and only one" axon. Some sources describe a fourth type of neuron, called an anaxonic neuron. The name suggests that it has no axon (an- = "without"), but this is not accurate. Anaxonic neurons are very small, and if you look through a microscope at the standard resolution used in histology (approximately 400X to 1000X total magnification), you will not be able to distinguish any process specifically as an axon or a dendrite. Any of those processes can function as an axon depending on the conditions at any given time. Nevertheless, even if they cannot be easily seen, and one specific process

is definitively the axon, these neurons have multiple processes and are therefore multipolar.

Neurons can also be classified on the basis of where they are found, who found them, what they do, or even what chemicals they use to communicate with each other. Some neurons referred to in this section on the nervous system are named on the basis of those sorts of classifications ([link]). For example, a multipolar neuron that has a very important role to play in a part of the brain called the cerebellum is known as a Purkinje (commonly pronounced per-KIN-gee) cell. It is named after the anatomist who discovered it (Jan Evangilista Purkinje, 1787–1869).

Other Neuron Classifications

Three examples of neurons that are classified on the basis of other criteria. (a) The pyramidal cell is a multipolar cell with a cell body that is shaped something like a pyramid. (b) The Purkinje cell in the cerebellum was named after the scientist who originally described it. (c) Olfactory neurons are named for the functional group with which they belong.



(a) Pyramidal cell of the cerebral cortex

(b) Purkinje cell of the cerebellar cortex

(c) Olfactory cells in the olfactory epithelium and olfactory bulbs

Glial Cells

Glial cells, or neuroglia or simply glia, are the other type of cell found in nervous tissue. They are considered to be supporting cells, and many functions are directed at helping neurons complete their function for communication. The name glia comes from the Greek word that means “glue,” and was coined by the German pathologist Rudolph Virchow, who wrote in 1856: “This connective substance, which is in the brain, the spinal cord, and the special sense nerves, is a kind of glue (neuroglia) in which the nervous elements are planted.” Today, research into nervous tissue has shown that there are many deeper roles that these cells play. And research may find much more about them in the future.

There are six types of glial cells. Four of them are found in the CNS and two are found in the PNS. [link] outlines some common characteristics and functions.

Glial Cell Types by Location and Basic Function		
CNS glia	PNS glia	Basic function
Astrocyte	Satellite cell	Support
Oligodendrocyte	Schwann cell	Insulation, myelination
Microglia	-	Immune surveillance and phagocytosis
Ependymal cell	-	Creating CSF

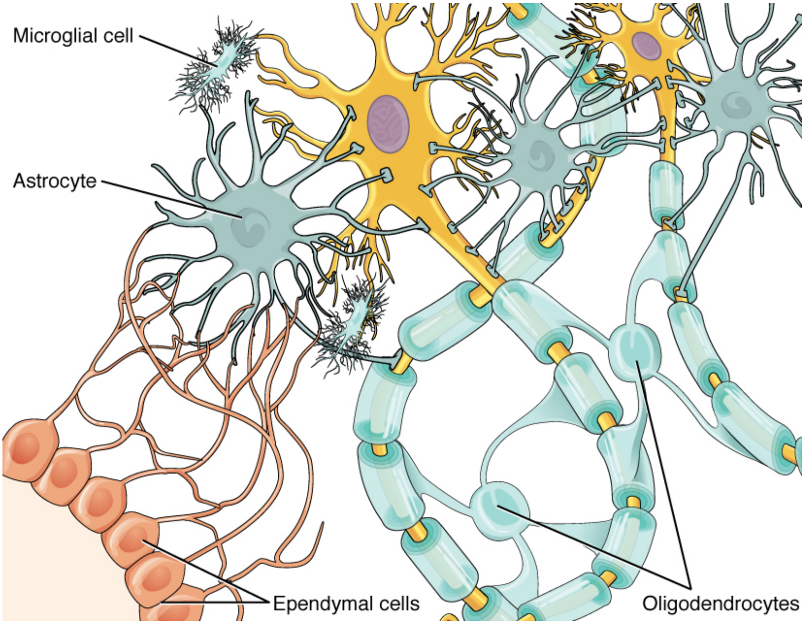
Glial Cells of the CNS

One cell providing support to neurons of the CNS is the **astrocyte**, so named because it appears to be star-shaped under the microscope (astro- = “star”). Astrocytes have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions). Those processes extend to interact with neurons, blood vessels, or

the connective tissue covering the CNS that is called the pia mater ([link]). Generally, they are supporting cells for the neurons in the central nervous system. Some ways in which they support neurons in the central nervous system are by maintaining the concentration of chemicals in the extracellular space, removing excess signaling molecules, reacting to tissue damage, and contributing to the **blood-brain barrier (BBB)**. The blood-brain barrier is a physiological barrier that keeps many substances that circulate in the rest of the body from getting into the central nervous system, restricting what can cross from circulating blood into the CNS. Nutrient molecules, such as glucose or amino acids, can pass through the BBB, but other molecules cannot. This actually causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the BBB as well as have an effect on the nervous system.

Glial Cells of the CNS

The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.



Like a few other parts of the body, the brain has a privileged blood supply. Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. Because of this, only specific types of molecules can enter the CNS. Glucose—the primary energy source—is allowed, as are amino acids. Water and some other small particles, like gases and ions, can enter. But most everything else cannot, including white blood cells, which are one of the body's main lines of defense. While this barrier protects the CNS from exposure to toxic or pathogenic substances, it also keeps out the cells that could protect the brain and spinal cord from disease and damage. The BBB also makes it harder for pharmaceuticals to be developed that can affect the nervous system. Aside from finding

efficacious substances, the means of delivery is also crucial.

Also found in CNS tissue is the **oligodendrocyte**, sometimes called just “oligo,” which is the glial cell type that insulates axons in the CNS. The name means “cell of a few branches” (oligo- = “few”; dendro- = “branches”; -cyte = “cell”). There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte will provide the myelin for multiple axon segments, either for the same axon or for separate axons. The function of myelin will be discussed below.

Microglia are, as the name implies, smaller than most of the other glial cells. Ongoing research into these cells, although not entirely conclusive, suggests that they may originate as white blood cells, called macrophages, that become part of the CNS during early development. While their origin is not conclusively determined, their function is related to what macrophages do in the rest of the body. When macrophages encounter diseased or damaged cells in the rest of the body, they ingest and digest those cells or the pathogens that cause disease. Microglia are the cells in the CNS that can do this in normal, healthy tissue, and they are therefore also referred to as CNS-resident macrophages.

The **ependymal cell** is a glial cell that filters blood to make **cerebrospinal fluid (CSF)**, the fluid that circulates through the CNS. Because of the privileged blood supply inherent in the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood. Ependymal cells line each **ventricle**, one of four central cavities that are remnants of the hollow center of the neural tube formed during the embryonic development of the brain. The **choroid plexus** is a specialized structure in the ventricles where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce cerebrospinal fluid. Because of this, ependymal cells can be considered a component of the BBB, or a place where the BBB breaks down. These glial cells appear similar to epithelial cells, making a single layer of cells with little intracellular space and tight connections between adjacent cells. They also have cilia on their apical surface to help move the CSF through the ventricular space. The relationship of these glial cells to the structure of the CNS is seen in [link].

Glial Cells of the PNS

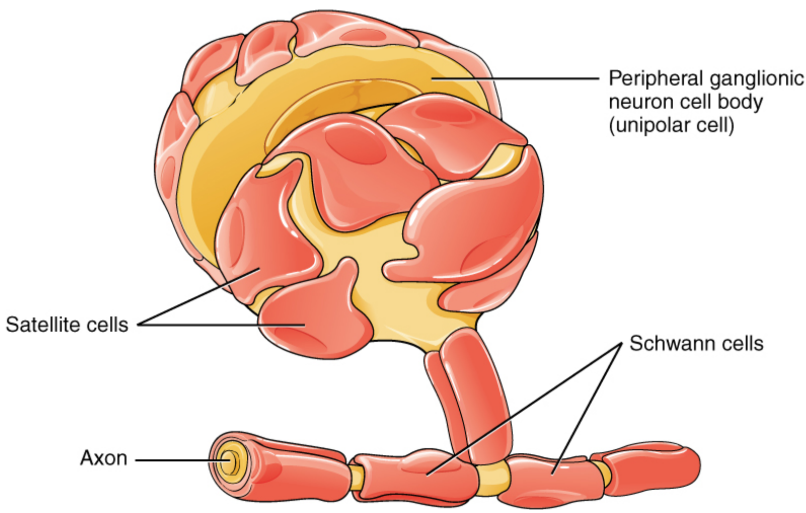
One of the two types of glial cells found in the PNS is the **satellite cell**. Satellite cells are found in sensory and autonomic ganglia, where they surround the cell bodies of neurons. This accounts for the name, based on their appearance under the

microscope. They provide support, performing similar functions in the periphery as astrocytes do in the CNS—except, of course, for establishing the BBB.

The second type of glial cell is the **Schwann cell**, which insulate axons with myelin in the periphery. Schwann cells are different than oligodendrocytes, in that a Schwann cell wraps around a portion of only one axon segment and no others. Oligodendrocytes have processes that reach out to multiple axon segments, whereas the entire Schwann cell surrounds just one axon segment. The nucleus and cytoplasm of the Schwann cell are on the edge of the myelin sheath. The relationship of these two types of glial cells to ganglia and nerves in the PNS is seen in [link].

Glial Cells of the PNS

The PNS has satellite cells and Schwann cells.



Myelin

The insulation for axons in the nervous system is provided by glial cells, oligodendrocytes in the CNS, and Schwann cells in the PNS. Whereas the manner in which either cell is associated with the axon segment, or segments, that it insulates is different, the means of myelinating an axon segment is mostly the same in the two situations. Myelin is a lipid-rich sheath that surrounds the axon and by doing so creates a **myelin sheath** that facilitates the transmission of electrical signals along the axon. The lipids are essentially the phospholipids of the glial cell membrane. Myelin, however, is more than just the membrane of the glial cell. It also includes important proteins that are integral to that membrane. Some of the proteins help to hold the layers of the glial cell membrane closely together.

The appearance of the myelin sheath can be thought of as similar to the pastry wrapped around a hot dog for "pigs in a blanket" or a similar food. The glial cell is wrapped around the axon several times with little to no cytoplasm between the glial cell layers. For oligodendrocytes, the rest of the cell is separate from the myelin sheath as a cell process extends back toward the cell body. A few other processes provide the same insulation for other axon segments in the area. For Schwann cells, the outermost layer of the cell membrane contains cytoplasm and the nucleus of the cell as a bulge on one side of the

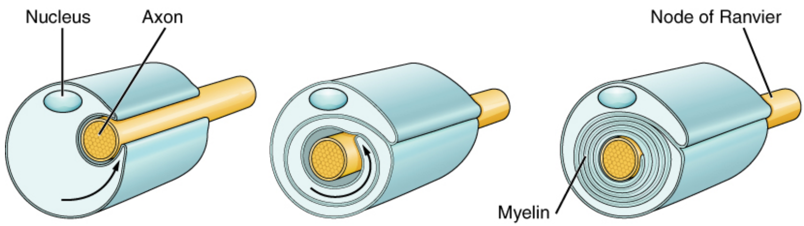
myelin sheath. During development, the glial cell is loosely or incompletely wrapped around the axon ([link]**a**). The edges of this loose enclosure extend toward each other, and one end tucks under the other. The inner edge wraps around the axon, creating several layers, and the other edge closes around the outside so that the axon is completely enclosed.

View the University of Michigan WebScope to see an electron micrograph of a cross-section of a myelinated nerve fiber. The axon contains microtubules and neurofilaments that are bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain to make them a deep, dark, black color, such as the multiple layers that are the myelin sheath?

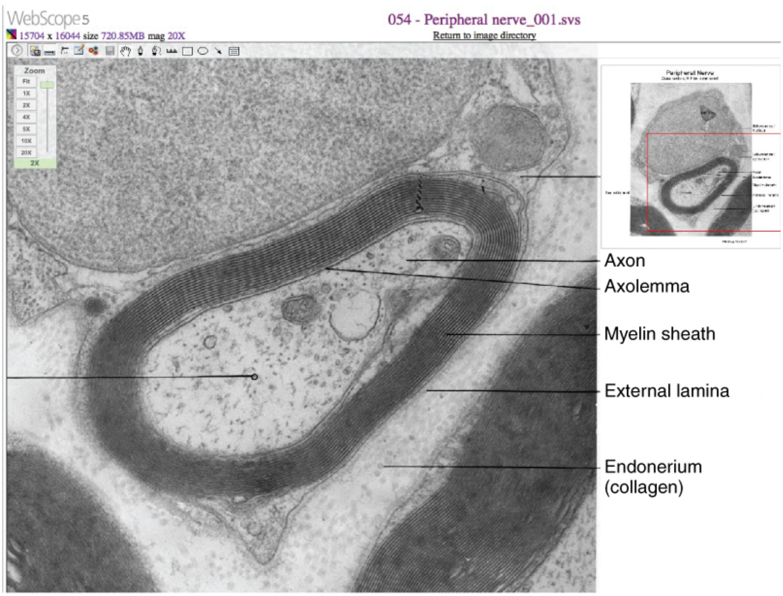
Myelin sheaths can extend for one or two millimeters, depending on the diameter of the axon. Axon diameters can be as small as 1 to 20 micrometers. Because a micrometer is 1/1000 of a millimeter, this means that the length of a myelin sheath can be 100–1000 times the diameter of the axon. [link], [link], and [link] show the myelin sheath surrounding an axon segment, but are not to scale. If the myelin sheath were drawn to scale, the neuron would have to be immense—possibly covering an entire wall of the room in which you are sitting.

The Process of Myelination

Myelinating glia wrap several layers of cell membrane around the cell membrane of an axon segment. A single Schwann cell insulates a segment of a peripheral nerve, whereas in the CNS, an oligodendrocyte may provide insulation for a few separate axon segments. EM × 1,460,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



(a)



(b)

Disorders of the…

Nervous Tissue

Several diseases can result from the demyelination of axons. The causes of these diseases are not the same; some have genetic causes, some are caused by pathogens, and others are the result of autoimmune disorders. Though the causes are varied, the results are largely similar. The myelin

insulation of axons is compromised, making electrical signaling slower.

Multiple sclerosis (MS) is one such disease. It is an example of an autoimmune disease. The antibodies produced by lymphocytes (a type of white blood cell) mark myelin as something that should not be in the body. This causes inflammation and the destruction of the myelin in the central nervous system. As the insulation around the axons is destroyed by the disease, scarring becomes obvious. This is where the name of the disease comes from; sclerosis means hardening of tissue, which is what a scar is. Multiple scars are found in the white matter of the brain and spinal cord. The symptoms of MS include both somatic and autonomic deficits. Control of the musculature is compromised, as is control of organs such as the bladder.

Guillain-Barré (pronounced gee-YAN bah-RAY) syndrome is an example of a demyelinating disease of the peripheral nervous system. It is also the result of an autoimmune reaction, but the inflammation is in peripheral nerves. Sensory symptoms or motor deficits are common, and autonomic failures can lead to changes in the heart rhythm or a drop in blood pressure, especially when standing, which causes dizziness.

Chapter Review

Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical signals. Glial cells are supporting cells, maintaining the environment around the neurons.

Neurons are polarized cells, based on the flow of electrical signals along their membrane. Signals are received at the dendrites, are passed along the cell body, and propagate along the axon towards the target, which may be another neuron, muscle tissue, or a gland. Many axons are insulated by a lipid-rich substance called myelin. Specific types of glial cells provide this insulation.

Several types of glial cells are found in the nervous system, and they can be categorized by the anatomical division in which they are found. In the CNS, astrocytes, oligodendrocytes, microglia, and ependymal cells are found. Astrocytes are important for maintaining the chemical environment around the neuron and are crucial for regulating the blood-brain barrier. Oligodendrocytes are the myelinating glia in the CNS. Microglia act as phagocytes and play a role in immune surveillance. Ependymal cells are responsible for filtering the blood to produce cerebrospinal fluid, which is a circulatory fluid that performs some of the functions of blood in the brain and spinal cord because of the BBB. In the PNS,

satellite cells are supporting cells for the neurons, and Schwann cells insulate peripheral axons.

Interactive Link Questions

Visit this site to learn about how nervous tissue is composed of neurons and glial cells. The neurons are dynamic cells with the ability to make a vast number of connections and to respond incredibly quickly to stimuli and to initiate movements based on those stimuli. They are the focus of intense research as failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Based on what this article says about neuron function, why wouldn’t they be helpful for plants or microorganisms?

Neurons enable thought, perception, and movement. Plants do not move, so they do not need this type of tissue. Microorganisms are too small to have a nervous system. Many are single-celled, and therefore have organelles for perception and movement.

View the University of Michigan Webscope to see an electron micrograph of a cross-section of

a myelinated nerve fiber. The axon contains microtubules and neurofilaments, bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain that makes them the deep, dark, black color, such as the multiple layers that are the myelin sheath?

Lipid membranes, such as the cell membrane and organelle membranes.

Review Questions

What type of glial cell provides myelin for the axons in a tract?

1. oligodendrocyte
2. astrocyte
3. Schwann cell
4. satellite cell

A

Which part of a neuron contains the nucleus?

1. dendrite
2. soma
3. axon
4. synaptic end bulb

B

Which of the following substances is least able to cross the blood-brain barrier?

1. water
2. sodium ions
3. glucose
4. white blood cells

D

What type of glial cell is the resident macrophage behind the blood-brain barrier?

1. microglia
2. astrocyte
3. Schwann cell
4. satellite cell

A

What two types of macromolecules are the main components of myelin?

1. carbohydrates and lipids
2. proteins and nucleic acids
3. lipids and proteins
4. carbohydrates and nucleic acids

C

Critical Thinking Questions

Multiple sclerosis is a demyelinating disease affecting the central nervous system. What type of cell would be the most likely target of this disease? Why?

The disease would target oligodendrocytes. In the CNS, oligodendrocytes provide the myelin for axons.

Which type of neuron, based on its shape, is best suited for relaying information directly

from one neuron to another? Explain why.

Bipolar cells, because they have one dendrite that receives input and one axon that provides output, would be a direct relay between two other cells.

Glossary

astrocyte
: glial cell type of the CNS that provides support for neurons and maintains the blood-brain barrier

axon hillock
: tapering of the neuron cell body that gives rise to the axon

axon segment
: single stretch of the axon insulated by myelin and bounded by nodes of Ranvier at either end (except for the first, which is after the initial segment, and the last, which is followed by the axon terminal)

axon terminal
: end of the axon, where there are usually several branches extending toward the target cell

axoplasm
: cytoplasm of an axon, which is different in composition than the cytoplasm of the neuronal cell body

bipolar
: shape of a neuron with two processes extending from the neuron cell body—the axon and one dendrite

blood-brain barrier (BBB)
: physiological barrier between the circulatory system and the central nervous system that establishes a privileged blood supply, restricting the flow of substances into the CNS

cerebrospinal fluid (CSF)
: circulatory medium within the CNS that is produced by ependymal cells in the choroid plexus filtering the blood

choroid plexus
: specialized structure containing ependymal cells that line blood capillaries and filter blood to produce CSF in the four ventricles of the brain

ependymal cell
: glial cell type in the CNS responsible for producing cerebrospinal fluid

initial segment

first part of the axon as it emerges from the axon hillock, where the electrical signals known as action potentials are generated

microglia
: glial cell type in the CNS that serves as the resident component of the immune system

multipolar
: shape of a neuron that has multiple processes —the axon and two or more dendrites

myelin sheath
: lipid-rich layer of insulation that surrounds an axon, formed by oligodendrocytes in the CNS and Schwann cells in the PNS; facilitates the transmission of electrical signals

node of Ranvier
: gap between two myelinated regions of an axon, allowing for strengthening of the electrical signal as it propagates down the axon

oligodendrocyte
: glial cell type in the CNS that provides the myelin insulation for axons in tracts

satellite cell
: glial cell type in the PNS that provides support for neurons in the ganglia

Schwann cell
: glial cell type in the PNS that provides the myelin insulation for axons in nerves

synapse
: narrow junction across which a chemical signal passes from neuron to the next, initiating a new electrical signal in the target cell

synaptic end bulb
: swelling at the end of an axon where neurotransmitter molecules are released onto a target cell across a synapse

unipolar
: shape of a neuron which has only one process that includes both the axon and dendrite

ventricle
: central cavity within the brain where CSF is produced and circulates

The Function of Nervous Tissue

By the end of this section, you will be able to:

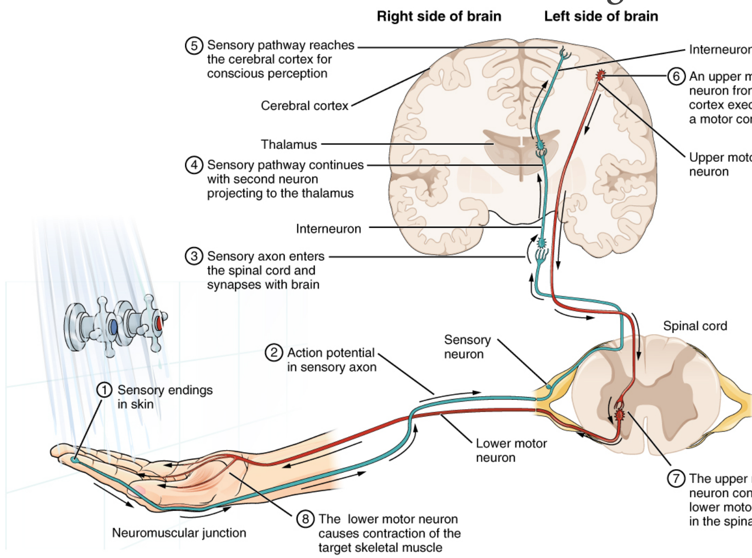
- Distinguish the major functions of the nervous system: sensation, integration, and response
- List the sequence of events in a simple sensory receptor–motor response pathway

Having looked at the components of nervous tissue, and the basic anatomy of the nervous system, next comes an understanding of how nervous tissue is capable of communicating within the nervous system. Before getting to the nuts and bolts of how this works, an illustration of how the components come together will be helpful. An example is summarized in [link].

Testing the Water

(1) The sensory neuron has endings in the skin that sense a stimulus such as water temperature. The strength of the signal that starts here is dependent on the strength of the stimulus. (2) The graded potential from the sensory endings, if strong enough, will initiate an action potential at the initial segment of the axon (which is immediately adjacent to the sensory endings in the skin). (3) The axon of the peripheral sensory neuron enters the spinal cord and contacts another neuron in the gray matter. The contact is a synapse where another graded potential is caused by the release of a chemical signal from the axon terminals. (4) An action potential is initiated at the initial segment of this neuron and

travels up the sensory pathway to a region of the brain called the thalamus. Another synapse passes the information along to the next neuron. (5) The sensory pathway ends when the signal reaches the cerebral cortex. (6) After integration with neurons in other parts of the cerebral cortex, a motor command is sent from the precentral gyrus of the frontal cortex. (7) The upper motor neuron sends an action potential down to the spinal cord. The target of the upper motor neuron is the dendrites of the lower motor neuron in the gray matter of the spinal cord. (8) The axon of the lower motor neuron emerges from the spinal cord in a nerve and connects to a muscle through a neuromuscular junction to cause contraction of the target muscle.



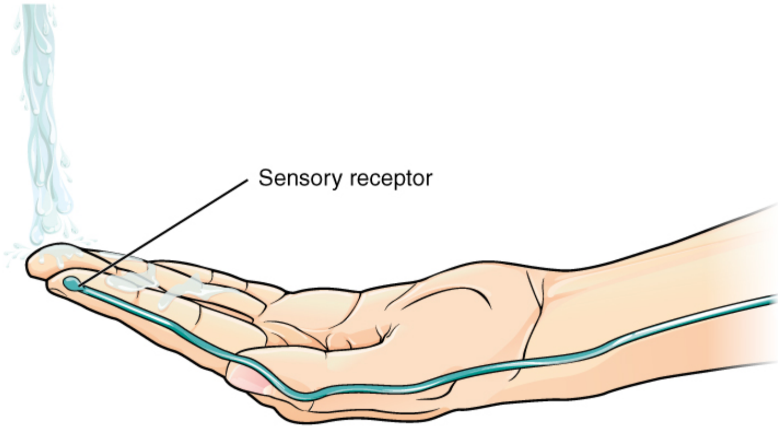
Imagine you are about to take a shower in the morning before going to school. You have turned on the faucet to start the water as you prepare to get in

the shower. After a few minutes, you expect the water to be a temperature that will be comfortable to enter. So you put your hand out into the spray of water. What happens next depends on how your nervous system interacts with the stimulus of the water temperature and what you do in response to that stimulus.

Found in the skin of your fingers or toes is a type of sensory receptor that is sensitive to temperature, called a **thermoreceptor**. When you place your hand under the shower ([link]), the cell membrane of the thermoreceptors changes its electrical state (voltage). The amount of change is dependent on the strength of the stimulus (how hot the water is). This is called a **graded potential**. If the stimulus is strong, the voltage of the cell membrane will change enough to generate an electrical signal that will travel down the axon. You have learned about this type of signaling before, with respect to the interaction of nerves and muscles at the neuromuscular junction. The voltage at which such a signal is generated is called the **threshold**, and the resulting electrical signal is called an **action potential**. In this example, the action potential travels—a process known as **propagation**—along the axon from the axon hillock to the axon terminals and into the synaptic end bulbs. When this signal reaches the end bulbs, it causes the release of a signaling molecule called a **neurotransmitter**.

The Sensory Input

Receptors in the skin sense the temperature of the water.



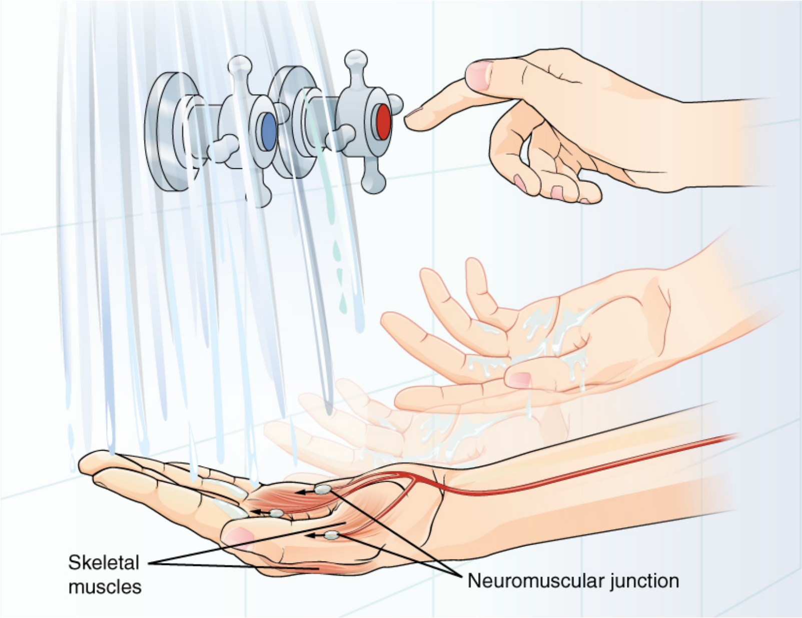
The neurotransmitter diffuses across the short distance of the synapse and binds to a receptor protein of the target neuron. When the molecular signal binds to the receptor, the cell membrane of the target neuron changes its electrical state and a new graded potential begins. If that graded potential is strong enough to reach threshold, the second neuron generates an action potential at its axon hillock. The target of this neuron is another neuron in the **thalamus** of the brain, the part of the CNS that acts as a relay for sensory information. At another synapse, neurotransmitter is released and binds to its receptor. The thalamus then sends the sensory information to the **cerebral cortex**, the outermost layer of gray matter in the brain, where conscious perception of that water temperature begins.

Within the cerebral cortex, information is processed

among many neurons, integrating the stimulus of the water temperature with other sensory stimuli, with your emotional state (you just aren't ready to wake up; the bed is calling to you), memories (perhaps of the lab notes you have to study before a quiz). Finally, a plan is developed about what to do, whether that is to turn the temperature up, turn the whole shower off and go back to bed, or step into the shower. To do any of these things, the cerebral cortex has to send a command out to your body to move muscles ([link]).

The Motor Response

On the basis of the sensory input and the integration in the CNS, a motor response is formulated and executed.



A region of the cortex is specialized for sending signals down to the spinal cord for movement. The

upper motor neuron is in this region, called the **precentral gyrus of the frontal cortex**, which has an axon that extends all the way down the spinal cord. At the level of the spinal cord at which this axon makes a synapse, a graded potential occurs in the cell membrane of a **lower motor neuron**. This second motor neuron is responsible for causing muscle fibers to contract. In the manner described in the chapter on muscle tissue, an action potential travels along the motor neuron axon into the periphery. The axon terminates on muscle fibers at the neuromuscular junction. Acetylcholine is released at this specialized synapse, which causes the muscle action potential to begin, following a large potential known as an end plate potential. When the lower motor neuron excites the muscle fiber, it contracts. All of this occurs in a fraction of a second, but this story is the basis of how the nervous system functions.

Career Connections

Neurophysiologist

Understanding how the nervous system works could be a driving force in your career. Studying neurophysiology is a very rewarding path to follow. It means that there is a lot of work to do, but the rewards are worth the effort.

The career path of a research scientist can be straightforward: college, graduate school,

postdoctoral research, academic research position at a university. A Bachelor's degree in science will get you started, and for neurophysiology that might be in biology, psychology, computer science, engineering, or neuroscience. But the real specialization comes in graduate school. There are many different programs out there to study the nervous system, not just neuroscience itself. Most graduate programs are doctoral, meaning that a Master's degree is not part of the work. These are usually considered five-year programs, with the first two years dedicated to course work and finding a research mentor, and the last three years dedicated to finding a research topic and pursuing that with a near single-mindedness. The research will usually result in a few publications in scientific journals, which will make up the bulk of a doctoral dissertation. After graduating with a Ph.D., researchers will go on to find specialized work called a postdoctoral fellowship within established labs. In this position, a researcher starts to establish their own research career with the hopes of finding an academic position at a research university. Other options are available if you are interested in how the nervous system works. Especially for neurophysiology, a medical degree might be more suitable so you can learn about the clinical applications of neurophysiology and possibly work with human subjects. An academic career is not a necessity. Biotechnology firms are eager to find motivated scientists ready to tackle the tough

questions about how the nervous system works so that therapeutic chemicals can be tested on some of the most challenging disorders such as Alzheimer's disease or Parkinson's disease, or spinal cord injury.
Others with a medical degree and a specialization in neuroscience go on to work directly with patients, diagnosing and treating mental disorders. You can do this as a psychiatrist, a neuropsychologist, a neuroscience nurse, or a neurodiagnostic technician, among other possible career paths.

Chapter Review

Sensation starts with the activation of a sensory ending, such as the thermoreceptor in the skin sensing the temperature of the water. The sensory endings in the skin initiate an electrical signal that travels along the sensory axon within a nerve into the spinal cord, where it synapses with a neuron in the gray matter of the spinal cord. The temperature information represented in that electrical signal is passed to the next neuron by a chemical signal that diffuses across the small gap of the synapse and initiates a new electrical signal in the target cell. That signal travels through the sensory pathway to

the brain, passing through the thalamus, where conscious perception of the water temperature is made possible by the cerebral cortex. Following integration of that information with other cognitive processes and sensory information, the brain sends a command back down to the spinal cord to initiate a motor response by controlling a skeletal muscle. The motor pathway is composed of two cells, the upper motor neuron and the lower motor neuron. The upper motor neuron has its cell body in the cerebral cortex and synapses on a cell in the gray matter of the spinal cord. The lower motor neuron is that cell in the gray matter of the spinal cord and its axon extends into the periphery where it synapses with a skeletal muscle in a neuromuscular junction.

Review Questions

If a thermoreceptor is sensitive to temperature sensations, what would a chemoreceptor be sensitive to?

1. light
2. sound
3. molecules
4. vibration

C

Which of these locations is where the greatest level of integration is taking place in the example of testing the temperature of the shower?

1. skeletal muscle
2. spinal cord
3. thalamus
4. cerebral cortex

D

How long does all the signaling through the sensory pathway, within the central nervous system, and through the motor command pathway take?

1. 1 to 2 minutes
2. 1 to 2 seconds
3. fraction of a second
4. varies with graded potential

C

What is the target of an upper motor neuron?

1. cerebral cortex

2. lower motor neuron
3. skeletal muscle
4. thalamus

B

Critical Thinking Questions

Sensory fibers, or pathways, are referred to as “afferent.” Motor fibers, or pathways, are referred to as “efferent.” What can you infer about the meaning of these two terms (afferent and efferent) in a structural or anatomical context?

Afferent means “toward,” as in sensory information traveling from the periphery into the CNS. Efferent means “away from,” as in motor commands that travel from the brain down the spinal cord and out into the periphery.

If a person has a motor disorder and cannot move their arm voluntarily, but their muscles have tone, which motor neuron—upper or

lower—is probably affected? Explain why.

The upper motor neuron would be affected because it is carrying the command from the brain down.

Glossary

action potential
: change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers

cerebral cortex
: outermost layer of gray matter in the brain, where conscious perception takes place

graded potential
: change in the membrane potential that varies in size, depending on the size of the stimulus that elicits it

lower motor neuron
: second neuron in the motor command pathway that is directly connected to the skeletal muscle

neurotransmitter
: chemical signal that is released from the

synaptic end bulb of a neuron to cause a change in the target cell

precentral gyrus of the frontal cortex
: region of the cerebral cortex responsible for generating motor commands, where the upper motor neuron cell body is located

propagation
: movement of an action potential along the length of an axon

thalamus
: region of the central nervous system that acts as a relay for sensory pathways

thermoreceptor
: type of sensory receptor capable of transducing temperature stimuli into neural action potentials

threshold
: membrane voltage at which an action potential is initiated

upper motor neuron
: first neuron in the motor command pathway with its cell body in the cerebral cortex that synapses on the lower motor neuron in the spinal cord

Introduction

class="introduction"

Human Nervous System

The ability to balance like an acrobat combines functions throughout the nervous system. The central and peripheral divisions coordinate control of the body using the senses of balance, body position, and touch on the soles of the feet. (credit: Rhett Sutphin)

Chapter Objectives

After studying this chapter, you will be able to:

- Relate the developmental processes of the embryonic nervous system to the adult structures
- Name the major regions of the adult nervous

system
- Locate regions of the cerebral cortex on the basis of anatomical landmarks common to all human brains
- Describe the regions of the spinal cord in cross-section
- List the cranial nerves in order of anatomical location and provide the central and peripheral connections
- List the spinal nerves by vertebral region and by which nerve plexus each supplies

The nervous system is responsible for controlling much of the body, both through somatic (voluntary) and autonomic (involuntary) functions. The structures of the nervous system must be described in detail to understand how many of these functions are possible. There is a physiological concept known as localization of function that states that certain structures are specifically responsible for prescribed functions. It is an underlying concept in all of anatomy and physiology, but the nervous system illustrates the concept very well.

Fresh, unstained nervous tissue can be described as gray or white matter, and within those two types of tissue it can be very hard to see any detail. However, as specific regions and structures have been described, they were related to specific

functions. Understanding these structures and the functions they perform requires a detailed description of the anatomy of the nervous system, delving deep into what the central and peripheral structures are.

The place to start this study of the nervous system is the beginning of the individual human life, within the womb. The embryonic development of the nervous system allows for a simple framework on which progressively more complicated structures can be built. With this framework in place, a thorough investigation of the nervous system is possible.

The Embryologic Perspective

By the end of this section, you will be able to:

- Describe the growth and differentiation of the neural tube
- Relate the different stages of development to the adult structures of the central nervous system
- Explain the expansion of the ventricular system of the adult brain from the central canal of the neural tube
- Describe the connections of the diencephalon and cerebellum on the basis of patterns of embryonic development

The brain is a complex organ composed of gray parts and white matter, which can be hard to distinguish. Starting from an embryologic perspective allows you to understand more easily how the parts relate to each other. The embryonic nervous system begins as a very simple structure—essentially just a straight line, which then gets increasingly complex. Looking at the development of the nervous system with a couple of early snapshots makes it easier to understand the whole complex system.

Many structures that appear to be adjacent in the adult brain are not connected, and the connections that exist may seem arbitrary. But there is an underlying order to the system that comes from how

different parts develop. By following the developmental pattern, it is possible to learn what the major regions of the nervous system are.

The Neural Tube

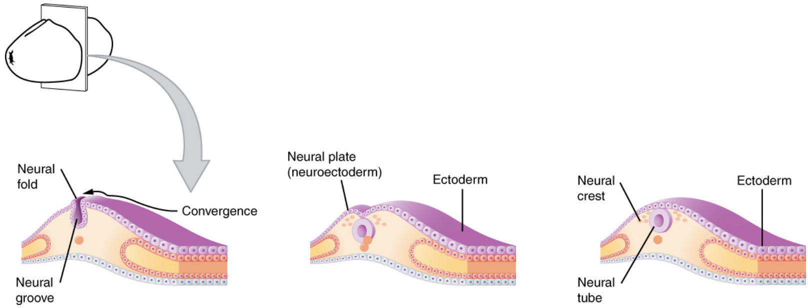
To begin, a sperm cell and an egg cell fuse to become a fertilized egg. The fertilized egg cell, or zygote, starts dividing to generate the cells that make up an entire organism. Sixteen days after fertilization, the developing embryo's cells belong to one of three germ layers that give rise to the different tissues in the body. The endoderm, or inner tissue, is responsible for generating the lining tissues of various spaces within the body, such as the mucosae of the digestive and respiratory systems. The mesoderm, or middle tissue, gives rise to most of the muscle and connective tissues. Finally the ectoderm, or outer tissue, develops into the integumentary system (the skin) and the nervous system. It is probably not difficult to see that the outer tissue of the embryo becomes the outer covering of the body. But how is it responsible for the nervous system?

As the embryo develops, a portion of the ectoderm differentiates into a specialized region of neuroectoderm, which is the precursor for the tissue of the nervous system. Molecular signals induce cells in this region to differentiate into the

neuroepithelium, forming a **neural plate**. The cells then begin to change shape, causing the tissue to buckle and fold inward ([link]). A **neural groove** forms, visible as a line along the dorsal surface of the embryo. The ridge-like edge on either side of the neural groove is referred as the **neural fold**. As the neural folds come together and converge, the underlying structure forms into a tube just beneath the ectoderm called the **neural tube**. Cells from the neural folds then separate from the ectoderm to form a cluster of cells referred to as the **neural crest**, which runs lateral to the neural tube. The neural crest migrates away from the nascent, or embryonic, central nervous system (CNS) that will form along the neural groove and develops into several parts of the peripheral nervous system (PNS), including the enteric nervous tissue. Many tissues that are not part of the nervous system also arise from the neural crest, such as craniofacial cartilage and bone, and melanocytes.

Early Embryonic Development of Nervous System

The neuroectoderm begins to fold inward to form the neural groove. As the two sides of the neural groove converge, they form the neural tube, which lies beneath the ectoderm. The anterior end of the neural tube will develop into the brain, and the posterior portion will become the spinal cord. The neural crest develops into peripheral structures.



At this point, the early nervous system is a simple, hollow tube. It runs from the anterior end of the embryo to the posterior end. Beginning at 25 days, the anterior end develops into the brain, and the posterior portion becomes the spinal cord. This is the most basic arrangement of tissue in the nervous system, and it gives rise to the more complex structures by the fourth week of development.

Primary Vesicles

As the anterior end of the neural tube starts to develop into the brain, it undergoes a couple of enlargements; the result is the production of sac-like vesicles. Similar to a child's balloon animal, the long, straight neural tube begins to take on a new shape. Three vesicles form at the first stage, which are called **primary vesicles**. These vesicles are given names that are based on Greek words, the main root word being *enkephalon*, which means "brain" (en- = "inside"; kephalon = "head"). The prefix to each generally corresponds to its position

along the length of the developing nervous system.

The **prosencephalon** (pros- = “in front”) is the forward-most vesicle, and the term can be loosely translated to mean **forebrain**. The **mesencephalon** (mes- = “middle”) is the next vesicle, which can be called the **midbrain**. The third vesicle at this stage is the **rhombencephalon**. The first part of this word is also the root of the word rhombus, which is a geometrical figure with four sides of equal length (a square is a rhombus with 90° angles). Whereas prosencephalon and mesencephalon translate into the English words forebrain and midbrain, there is not a word for “four-sided-figure-brain.” However, the third vesicle can be called the **hindbrain**. One way of thinking about how the brain is arranged is to use these three regions—forebrain, midbrain, and hindbrain—which are based on the primary vesicle stage of development ([link]**a**).

Secondary Vesicles

The brain continues to develop, and the vesicles differentiate further (see [link]**b**). The three primary vesicles become five **secondary vesicles**. The prosencephalon enlarges into two new vesicles called the **telencephalon** and the **diencephalon**. The telecephalon will become the cerebrum. The diencephalon gives rise to several adult structures; two that will be important are the thalamus and the

hypothalamus. In the embryonic diencephalon, a structure known as the eye cup develops, which will eventually become the retina, the nervous tissue of the eye called the retina. This is a rare example of nervous tissue developing as part of the CNS structures in the embryo, but becoming a peripheral structure in the fully formed nervous system.

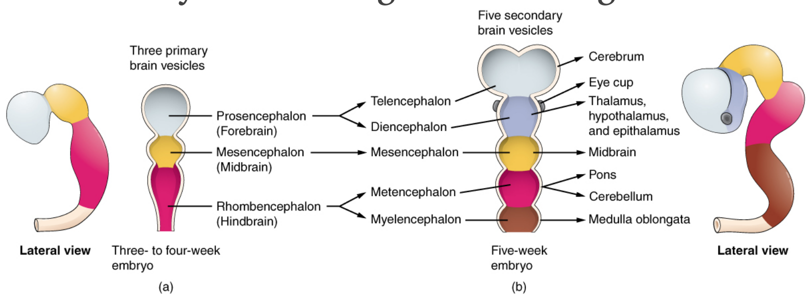
The mesencephalon does not differentiate into any finer divisions. The midbrain is an established region of the brain at the primary vesicle stage of development and remains that way. The rest of the brain develops around it and constitutes a large percentage of the mass of the brain. Dividing the brain into forebrain, midbrain, and hindbrain is useful in considering its developmental pattern, but the midbrain is a small proportion of the entire brain, relatively speaking.

The rhombencephalon develops into the **metencephalon** and **myelencephalon**. The metencephalon corresponds to the adult structure known as the pons and also gives rise to the cerebellum. The cerebellum (from the Latin meaning “little brain”) accounts for about 10 percent of the mass of the brain and is an important structure in itself. The most significant connection between the cerebellum and the rest of the brain is at the pons, because the pons and cerebellum develop out of the same vesicle. The myelencephalon corresponds to the adult structure

known as the medulla oblongata. The structures that come from the mesencephalon and rhombencephalon, except for the cerebellum, are collectively considered the **brain stem**, which specifically includes the midbrain, pons, and medulla.

Primary and Secondary Vesicle Stages of Development

The embryonic brain develops complexity through enlargements of the neural tube called vesicles; (a) The primary vesicle stage has three regions, and (b) the secondary vesicle stage has five regions.



Watch this animation to examine the development of the brain, starting with the neural tube. As the

anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?

Spinal Cord Development

While the brain is developing from the anterior neural tube, the spinal cord is developing from the posterior neural tube. However, its structure does not differ from the basic layout of the neural tube. It is a long, straight cord with a small, hollow space down the center. The neural tube is defined in terms of its anterior versus posterior portions, but it also has a dorsal–ventral dimension. As the neural tube separates from the rest of the ectoderm, the side closest to the surface is dorsal, and the deeper side is ventral.

As the spinal cord develops, the cells making up the wall of the neural tube proliferate and differentiate

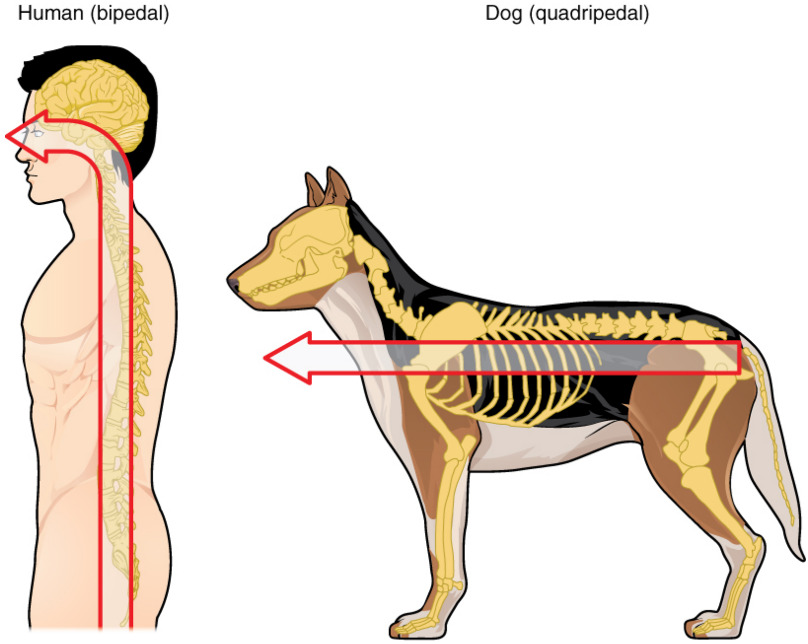
into the neurons and glia of the spinal cord. The dorsal tissues will be associated with sensory functions, and the ventral tissues will be associated with motor functions.

Relating Embryonic Development to the Adult Brain

Embryonic development can help in understanding the structure of the adult brain because it establishes a framework on which more complex structures can be built. First, the neural tube establishes the anterior–posterior dimension of the nervous system, which is called the **neuraxis**. The embryonic nervous system in mammals can be said to have a standard arrangement. Humans (and other primates, to some degree) make this complicated by standing up and walking on two legs. The anterior–posterior dimension of the neuraxis overlays the superior–inferior dimension of the body. However, there is a major curve between the brain stem and forebrain, which is called the **cephalic flexure**. Because of this, the neuraxis starts in an inferior position—the end of the spinal cord—and ends in an anterior position, the front of the cerebrum. If this is confusing, just imagine a four-legged animal standing up on two legs. Without the flexure in the brain stem, and at the top of the neck, that animal would be looking straight up instead of straight in front ([link]).

Human Neuraxis

The mammalian nervous system is arranged with the neural tube running along an anterior to posterior axis, from nose to tail for a four-legged animal like a dog. Humans, as two-legged animals, have a bend in the neuraxis between the brain stem and the diencephalon, along with a bend in the neck, so that the eyes and the face are oriented forward.



In summary, the primary vesicles help to establish the basic regions of the nervous system: forebrain, midbrain, and hindbrain. These divisions are useful in certain situations, but they are not equivalent regions. The midbrain is small compared with the hindbrain and particularly the forebrain. The secondary vesicles go on to establish the major

regions of the adult nervous system that will be followed in this text. The telencephalon is the cerebrum, which is the major portion of the human brain. The diencephalon continues to be referred to by this Greek name, because there is no better term for it (dia- = "through"). The diencephalon is between the cerebrum and the rest of the nervous system and can be described as the region through which all projections have to pass between the cerebrum and everything else. The brain stem includes the midbrain, pons, and medulla, which correspond to the mesencephalon, metencephalon, and myelencephalon. The cerebellum, being a large portion of the brain, is considered a separate region. [link] connects the different stages of development to the adult structures of the CNS.

One other benefit of considering embryonic development is that certain connections are more obvious because of how these adult structures are related. The retina, which began as part of the diencephalon, is primarily connected to the diencephalon. The eyes are just inferior to the anterior-most part of the cerebrum, but the optic nerve extends back to the thalamus as the optic tract, with branches into a region of the hypothalamus. There is also a connection of the optic tract to the midbrain, but the mesencephalon is adjacent to the diencephalon, so that is not difficult to imagine. The cerebellum originates out of the metencephalon, and its largest white matter

connection is to the pons, also from the metencephalon. There are connections between the cerebellum and both the medulla and midbrain, which are adjacent structures in the secondary vesicle stage of development. In the adult brain, the cerebellum seems close to the cerebrum, but there is no direct connection between them.

Another aspect of the adult CNS structures that relates to embryonic development is the ventricles—open spaces within the CNS where cerebrospinal fluid circulates. They are the remnant of the hollow center of the neural tube. The four ventricles and the tubular spaces associated with them can be linked back to the hollow center of the embryonic brain (see [link]).

Stages of Embryonic Development

Neural tube	Primary vesicle stage	Secondary vesicle stage	Adult structures	Ventricles
Anterior neural tube	Prosencephalon	Telencephalon	Cerebrum	Lateral ventricles
Anterior	Prosencephalon	Diencephalon	Diencephalon	Third

neural tube				ventricle
Anterior neural tube	Mesencephalon	Mesencephalon	Midbrain	Cerebral aqueduct
Anterior neural tube	Rhombencephalon	Metencephalon	Pons cerebellum	Fourth ventricle
Anterior neural tube	Rhombencephalon	Myelencephalon	Medulla	Fourth ventricle
Posterior neural tube			Spinal cord	Central canal

Disorders of the…

Nervous System

Early formation of the nervous system depends on the formation of the neural tube. A groove forms along the dorsal surface of the embryo, which becomes deeper until its edges meet and close off to form the tube. If this fails to happen, especially in the posterior region where the spinal cord forms, a developmental defect called spina bifida occurs. The closing of the neural tube is important for more than just the proper formation of the nervous system. The surrounding tissues are dependent on the correct development of the tube. The connective tissues surrounding the CNS can be

involved as well.

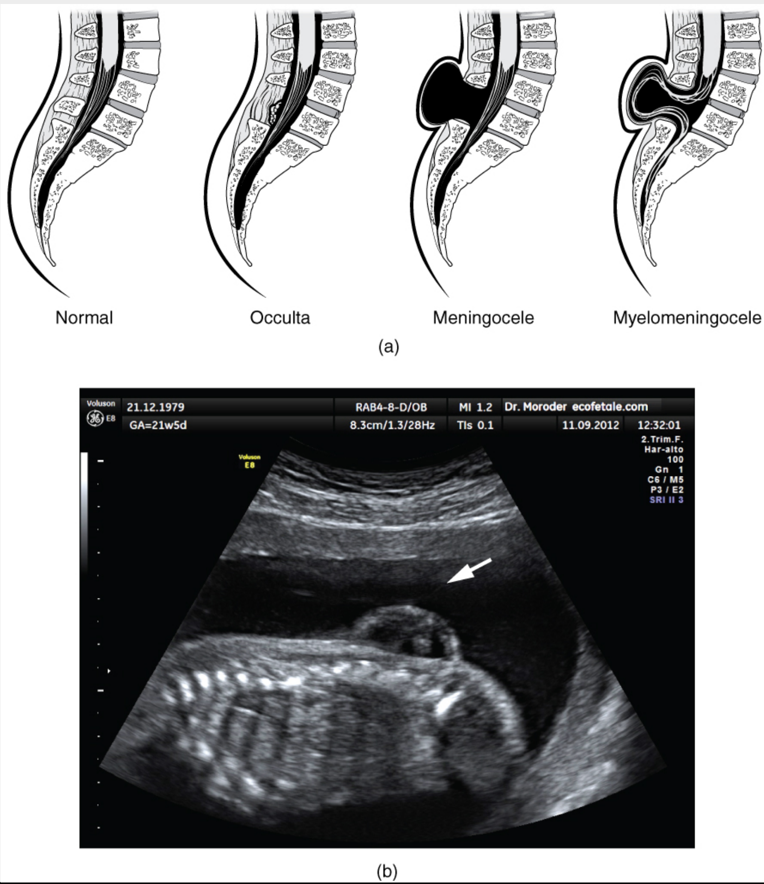
There are three classes of this disorder: occulta, meningocele, and myelomeningocele ([link]). The first type, spina bifida occulta, is the mildest because the vertebral bones do not fully surround the spinal cord, but the spinal cord itself is not affected. No functional differences may be noticed, which is what the word occulta means; it is hidden spina bifida. The other two types both involve the formation of a cyst—a fluid-filled sac of the connective tissues that cover the spinal cord called the meninges. “Meningocele” means that the meninges protrude through the spinal column but nerves may not be involved and few symptoms are present, though complications may arise later in life. “Myelomeningocele” means that the meninges protrude and spinal nerves are involved, and therefore severe neurological symptoms can be present.

Often surgery to close the opening or to remove the cyst is necessary. The earlier that surgery can be performed, the better the chances of controlling or limiting further damage or infection at the opening. For many children with meningocele, surgery will alleviate the pain, although they may experience some functional loss. Because the myelomeningocele form of spina bifida involves more extensive damage to the nervous tissue, neurological damage may persist, but symptoms can often be handled. Complications of the spinal cord may present later in life, but overall life

expectancy is not reduced.

Spinal Bifida

(a) Spina bifida is a birth defect of the spinal cord caused when the neural tube does not completely close, but the rest of development continues. The result is the emergence of meninges and neural tissue through the vertebral column. (b) Fetal myelomeningocele is evident in this ultrasound taken at 21 weeks.



Watch this video to learn about the white matter in the cerebrum that develops during childhood and adolescence. This is a composite of MRI images taken of the brains of people from 5 years of age through 20 years of age, demonstrating how the cerebrum changes. As the color changes to blue, the ratio of gray matter to white matter changes. The caption for the video describes it as “less gray matter,” which is another way of saying “more white matter.” If the brain does not finish developing until approximately 20 years of age, can teenagers be held responsible for behaving badly?

Chapter Review

The development of the nervous system starts early in embryonic development. The outer layer of the embryo, the ectoderm, gives rise to the skin and the

nervous system. A specialized region of this layer, the neuroectoderm, becomes a groove that folds in and becomes the neural tube beneath the dorsal surface of the embryo. The anterior end of the neural tube develops into the brain, and the posterior region becomes the spinal cord. Tissues at the edges of the neural groove, when it closes off, are called the neural crest and migrate through the embryo to give rise to PNS structures as well as some non-nervous tissues.

The brain develops from this early tube structure and gives rise to specific regions of the adult brain. As the neural tube grows and differentiates, it enlarges into three vesicles that correspond to the forebrain, midbrain, and hindbrain regions of the adult brain. Later in development, two of these three vesicles differentiate further, resulting in five vesicles. Those five vesicles can be aligned with the four major regions of the adult brain. The cerebrum is formed directly from the telencephalon. The diencephalon is the only region that keeps its embryonic name. The mesencephalon, metencephalon, and myelencephalon become the brain stem. The cerebellum also develops from the metencephalon and is a separate region of the adult brain.

The spinal cord develops out of the rest of the neural tube and retains the tube structure, with the nervous tissue thickening and the hollow center

becoming a very small central canal through the cord. The rest of the hollow center of the neural tube corresponds to open spaces within the brain called the ventricles, where cerebrospinal fluid is found.

Interactive Link Questions

Watch this animation to examine the development of the brain, starting with the neural tube. As the anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?

The three regions (forebrain, midbrain, and hindbrain) appear to be approximately equal in size when they are first established, but the midbrain in the adult is much smaller than the

others—suggesting that it does not increase in size nearly as much as the forebrain or hindbrain.

Watch this video to learn about the white matter in the cerebrum that develops during childhood and adolescence. This is a composite of MRI images taken of the brains of people from 5 years of age through 20 years of age, demonstrating how the cerebrum changes. As the color changes to blue, the ratio of gray matter to white matter changes. The caption for the video describes it as “less gray matter,” which is another way of saying “more white matter.” If the brain does not finish developing until approximately 20 years of age, can teenagers be held responsible for behaving badly?

This is really a matter of opinion, but there are ethical issues to consider when a teenager’s behavior results in legal trouble.

Multiple Choice

Aside from the nervous system, which other

organ system develops out of the ectoderm?

1. digestive
2. respiratory
3. integumentary
4. urinary

C

Which primary vesicle of the embryonic nervous system does not differentiate into more vesicles at the secondary stage?

1. prosencephalon
2. mesencephalon
3. diencephalon
4. rhombencephalon

B

Which adult structure(s) arises from the diencephalon?

1. thalamus, hypothalamus, retina
2. midbrain, pons, medulla
3. pons and cerebellum
4. cerebrum

A

Which non-nervous tissue develops from the neuroectoderm?

1. respiratory mucosa
2. vertebral bone
3. digestive lining
4. craniofacial bone

D

Which structure is associated with the embryologic development of the peripheral nervous system?

1. neural crest
2. neuraxis
3. rhombencephalon
4. neural tube

A

Critical Thinking Questions

Studying the embryonic development of the nervous system makes it easier to understand the complexity of the adult nervous system. Give one example of how development in the embryonic nervous system explains a more complex structure in the adult nervous system.

The retina, a PNS structure in the adult, grows from the diencephalon in the embryonic nervous system. The mature connections from the retina through the optic nerve/tract are to the hypothalamus and thalamus of the diencephalon, and to the midbrain, which developed directly adjacent to the diencephalon as the mesencephalon in the embryo.

What happens in development that suggests that there is a special relationship between the skeletal structure of the head and the nervous system?

The neural crest gives rise to PNS structures (such as ganglia) and also to cartilage and bone of the face and cranium.

Glossary

brain stem

region of the adult brain that includes the midbrain, pons, and medulla oblongata and develops from the mesencephalon, metencephalon, and myelencephalon of the embryonic brain

cephalic flexure
: curve in midbrain of the embryo that positions the forebrain ventrally

diencephalon
: region of the adult brain that retains its name from embryonic development and includes the thalamus and hypothalamus

forebrain
: anterior region of the adult brain that develops from the prosencephalon and includes the cerebrum and diencephalon

hindbrain
: posterior region of the adult brain that develops from the rhombencephalon and includes the pons, medulla oblongata, and cerebellum

mesencephalon
: primary vesicle of the embryonic brain that does not significantly change through the rest of embryonic development and becomes the midbrain

metencephalon
: secondary vesicle of the embryonic brain that develops into the pons and the cerebellum

midbrain
: middle region of the adult brain that develops from the mesencephalon

myelencephalon
: secondary vesicle of the embryonic brain that develops into the medulla

neural crest
: tissue that detaches from the edges of the neural groove and migrates through the embryo to develop into peripheral structures of both nervous and non-nervous tissues

neural fold
: elevated edge of the neural groove

neural groove
: region of the neural plate that folds into the dorsal surface of the embryo and closes off to become the neural tube

neural plate
: thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

neural tube
: precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

neuraxis
: central axis to the nervous system, from the posterior to anterior ends of the neural tube; the inferior tip of the spinal cord to the anterior surface of the cerebrum

primary vesicle
: initial enlargements of the anterior neural tube during embryonic development that develop into the forebrain, midbrain, and hindbrain

prosencephalon
: primary vesicle of the embryonic brain that develops into the forebrain, which includes the cerebrum and diencephalon

rhombencephalon
: primary vesicle of the embryonic brain that develops into the hindbrain, which includes the pons, cerebellum, and medulla

secondary vesicle
: five vesicles that develop from primary vesicles, continuing the process of differentiation of the embryonic brain

telencephalon

secondary vesicle of the embryonic brain that develops into the cerebrum

The Central Nervous System
By the end of this section, you will be able to:

- Name the major regions of the adult brain
- Describe the connections between the cerebrum and brain stem through the diencephalon, and from those regions into the spinal cord
- Recognize the complex connections within the subcortical structures of the basal nuclei
- Explain the arrangement of gray and white matter in the spinal cord

The brain and the spinal cord are the central nervous system, and they represent the main organs of the nervous system. The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. A person's conscious experiences are based on neural activity in the brain. The regulation of homeostasis is governed by a specialized region in the brain. The coordination of reflexes depends on the integration of sensory and motor pathways in the spinal cord.

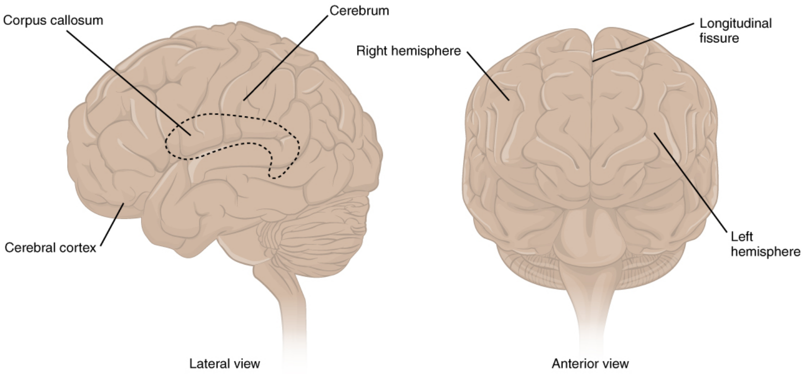
The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum** ([link]). The wrinkled portion is the

cerebral cortex, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, a right and left **cerebral hemisphere**. Deep within the cerebrum, the white matter of the **corpus callosum** provides the major pathway for communication between the two hemispheres of the cerebral cortex.

The Cerebrum

The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.



Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning “bark of a tree”) and several deep

nuclei that belong to three important functional groups. The **basal nuclei** are responsible for cognitive processing, the most important function being that associated with planning movements. The **basal forebrain** contains nuclei that are important in learning and memory. The **limbic cortex** is the region of the cerebral cortex that is part of the **limbic system**, a collection of structures involved in emotion, memory, and behavior.

Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the cerebral cortex. This thin, extensive region of wrinkled gray matter is responsible for the higher functions of the nervous system. A **gyrus** (plural = gyri) is the ridge of one of those wrinkles, and a **sulcus** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex.

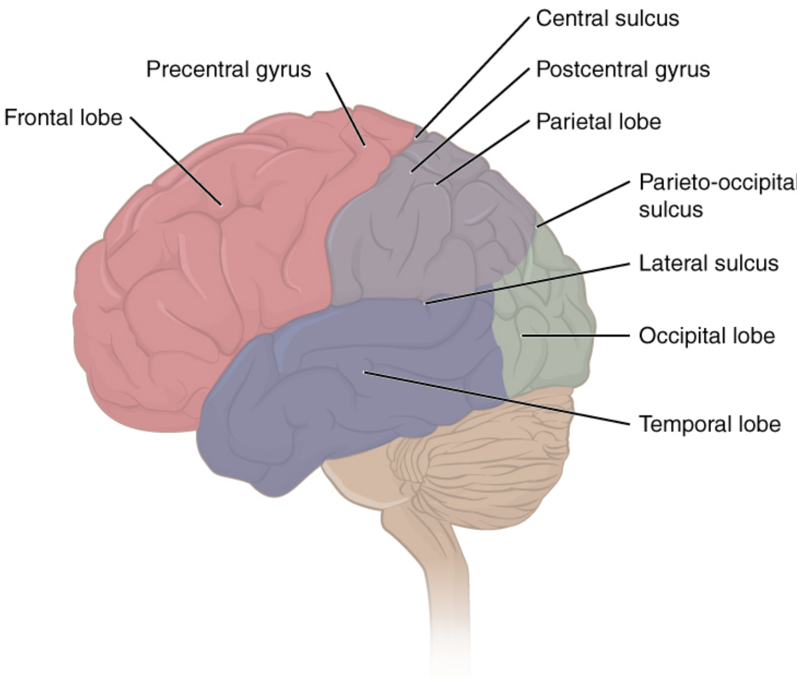
The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter.

The folding of the cortex maximizes the amount of

gray matter in the cranial cavity. During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone’s brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes ([link]). The **lateral sulcus** that separates the **temporal lobe** from the other regions is one such landmark. Superior to the lateral sulcus are the **parietal lobe** and **frontal lobe**, which are separated from each other by the **central sulcus**. The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an obvious landmark separating the parietal and occipital lobes is called the **parieto-occipital sulcus**. The fact that there is no obvious anatomical border between these lobes is consistent with the functions of these regions being interrelated.

Lobes of the Cerebral Cortex

The cerebral cortex is divided into four lobes. Extensive folding increases the surface area available for cerebral functions.



Different regions of the cerebral cortex can be associated with particular functions, a concept known as localization of function. In the early 1900s, a German neuroscientist named Korbinian Brodmann performed an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex and divided the cortex into 52 separate regions on the basis of the histology of the cortex. His work resulted in a system of classification known as **Brodmann's areas**, which is still used today to describe the anatomical distinctions within the cortex ([link]). The results from Brodmann's work on the anatomy align very well with the functional differences within the cortex. Areas 17 and 18 in the occipital lobe are

responsible for primary visual perception. That visual information is complex, so it is processed in the temporal and parietal lobes as well.

The temporal lobe is associated with primary auditory sensation, known as Brodmann's areas 41 and 42 in the superior temporal lobe. Because regions of the temporal lobe are part of the limbic system, memory is an important function associated with that lobe. Memory is essentially a sensory function; memories are recalled sensations such as the smell of Mom's baking or the sound of a barking dog. Even memories of movement are really the memory of sensory feedback from those movements, such as stretching muscles or the movement of the skin around a joint. Structures in the temporal lobe are responsible for establishing long-term memory, but the ultimate location of those memories is usually in the region in which the sensory perception was processed.

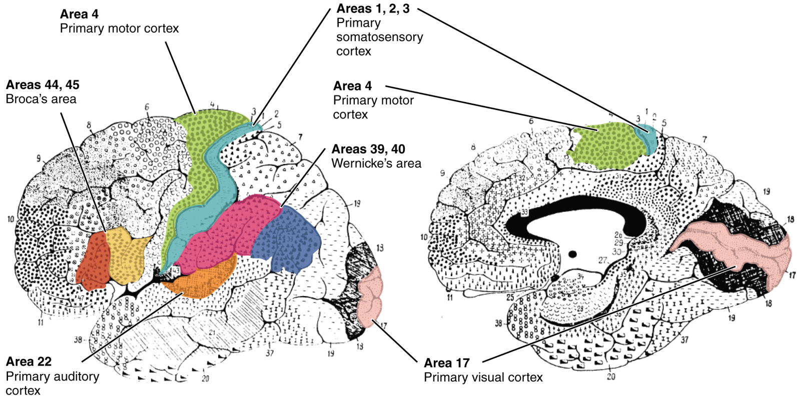
The main sensation associated with the parietal lobe is **somatosensation**, meaning the general sensations associated with the body. Posterior to the central sulcus is the **postcentral gyrus**, the primary somatosensory cortex, which is identified as Brodmann's areas 1, 2, and 3. All of the tactile senses are processed in this area, including touch, pressure, tickle, pain, itch, and vibration, as well as more general senses of the body such as **proprioception** and **kinesthesia**, which are the

senses of body position and movement, respectively.

Anterior to the central sulcus is the frontal lobe, which is primarily associated with motor functions. The **precentral gyrus** is the primary motor cortex. Cells from this region of the cerebral cortex are the upper motor neurons that instruct cells in the spinal cord to move skeletal muscles. Anterior to this region are a few areas that are associated with planned movements. The **premotor area** is responsible for thinking of a movement to be made. The **frontal eye fields** are important in eliciting eye movements and in attending to visual stimuli. **Broca's area** is responsible for the production of language, or controlling movements responsible for speech; in the vast majority of people, it is located only on the left side. Anterior to these regions is the **prefrontal lobe**, which serves cognitive functions that can be the basis of personality, short-term memory, and consciousness. The prefrontal lobotomy is an outdated mode of treatment for personality disorders (psychiatric conditions) that profoundly affected the personality of the patient.

Brodmann's Areas of the Cerebral Cortex

Brodmann mapping of functionally distinct regions of the cortex was based on its cytoarchitecture at a microscopic level.



Brodmann's cytotechtonic map (1909):
Lateral surface

Brodmann's cytotechtonic map (1909):
Medial surface

Subcortical structures

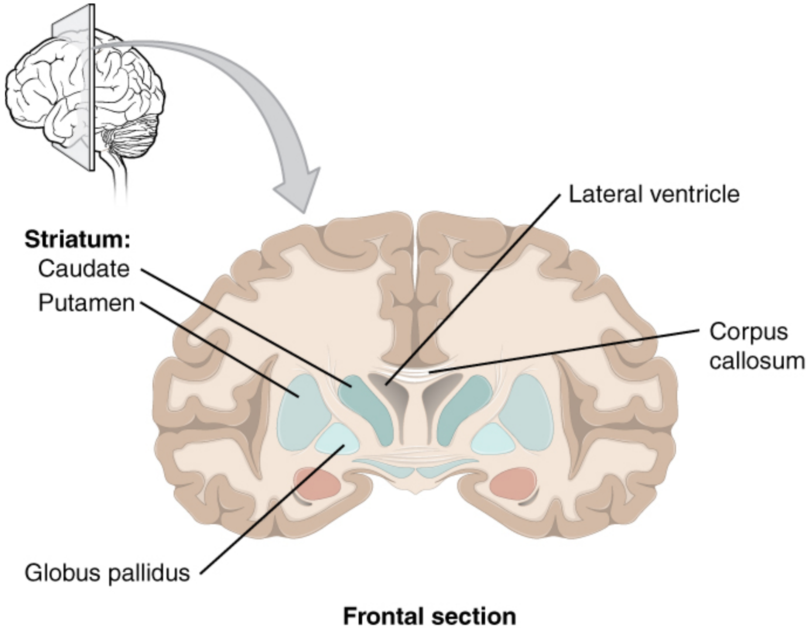
Beneath the cerebral cortex are sets of nuclei known as **subcortical nuclei** that augment cortical processes. The nuclei of the basal forebrain serve as the primary location for acetylcholine production, which modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain. The **hippocampus** and **amygdala** are medial-lobe structures that, along with the adjacent cortex, are involved in long-term memory formation and emotional responses. The basal nuclei are a set of nuclei in the cerebrum responsible for comparing cortical processing with the general state of activity in the nervous system to influence the likelihood of movement taking place. For example, while a student is sitting in a classroom listening to a lecture, the basal nuclei will

keep the urge to jump up and scream from actually happening. (The basal nuclei are also referred to as the basal ganglia, although that is potentially confusing because the term ganglia is typically used for peripheral structures.)

The major structures of the basal nuclei that control movement are the **caudate**, **putamen**, and **globus pallidus**, which are located deep in the cerebrum. The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe. The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the **striatum**. The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively. These nuclei are depicted in a frontal section of the brain in [link].

Frontal Section of Cerebral Cortex and Basal Nuclei

The major components of the basal nuclei, shown in a frontal section of the brain, are the caudate (just lateral to the lateral ventricle), the putamen (inferior to the caudate and separated by the large white-matter structure called the internal capsule), and the globus pallidus (medial to the putamen).

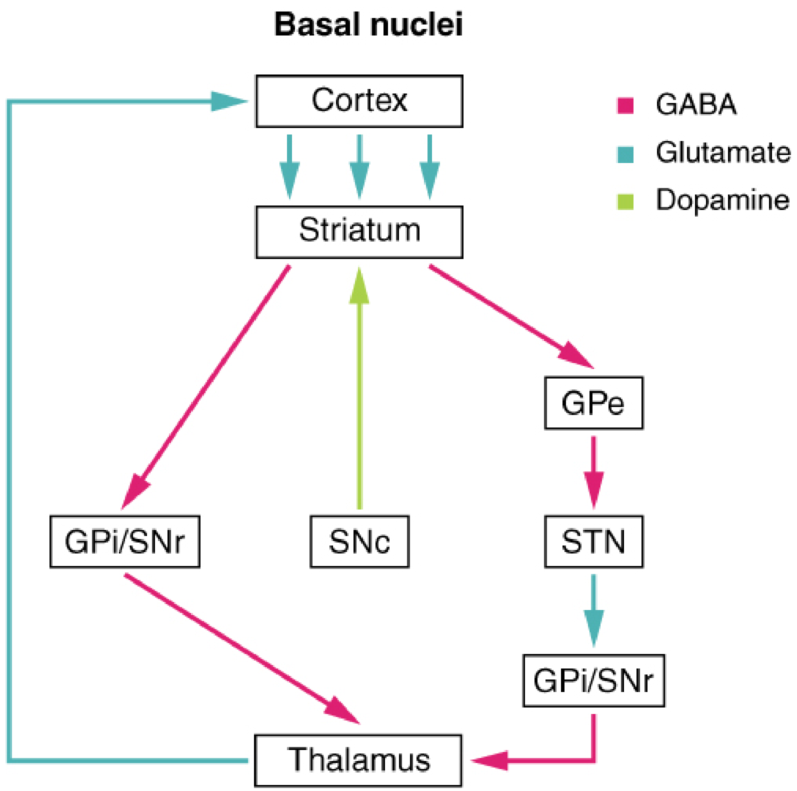


The basal nuclei in the cerebrum are connected with a few more nuclei in the brain stem that together act as a functional group that forms a motor pathway. Two streams of information processing take place in the basal nuclei. All input to the basal nuclei is from the cortex into the striatum ([link]). The **direct pathway** is the projection of axons from the striatum to the globus pallidus internal segment (GPi) and the **substantia nigra pars reticulata** (SNr). The GPi/SNr then projects to the thalamus, which projects back to the cortex. The **indirect pathway** is the projection of axons from the striatum to the globus pallidus external segment (GPe), then to the subthalamic nucleus (STN), and finally to GPi/SNr. The two streams both target the GPi/SNr, but one has a direct projection and the

other goes through a few intervening nuclei. The direct pathway causes the **disinhibition** of the thalamus (inhibition of one cell on a target cell that then inhibits the first cell), whereas the indirect pathway causes, or reinforces, the normal inhibition of the thalamus. The thalamus then can either excite the cortex (as a result of the direct pathway) or fail to excite the cortex (as a result of the indirect pathway).

Connections of Basal Nuclei

Input to the basal nuclei is from the cerebral cortex, which is an excitatory connection releasing glutamate as a neurotransmitter. This input is to the striatum, or the caudate and putamen. In the direct pathway, the striatum projects to the internal segment of the globus pallidus and the substantia nigra pars reticulata (GPi/SNr). This is an inhibitory pathway, in which GABA is released at the synapse, and the target cells are hyperpolarized and less likely to fire. The output from the basal nuclei is to the thalamus, which is an inhibitory projection using GABA.



The switch between the two pathways is the **substantia nigra pars compacta**, which projects to the striatum and releases the neurotransmitter dopamine. Dopamine receptors are either excitatory (D1-type receptors) or inhibitory (D2-type receptors). The direct pathway is activated by dopamine, and the indirect pathway is inhibited by dopamine. When the substantia nigra pars compacta is firing, it signals to the basal nuclei that the body is in an active state, and movement will be more likely. When the substantia nigra pars compacta is silent, the body is in a passive state, and movement is inhibited. To illustrate this situation, while a

student is sitting listening to a lecture, the substantia nigra pars compacta would be silent and the student less likely to get up and walk around. Likewise, while the professor is lecturing, and walking around at the front of the classroom, the professor’s substantia nigra pars compacta would be active, in keeping with his or her activity level.

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

Everyday Connections

The Myth of Left Brain/Right Brain

There is a persistent myth that people are “right-brained” or “left-brained,” which is an oversimplification of an important concept about the cerebral hemispheres. There is some lateralization of function, in which the left side of the brain is devoted to language function and the

right side is devoted to spatial and nonverbal reasoning. Whereas these functions are predominantly associated with those sides of the brain, there is no monopoly by either side on these functions. Many pervasive functions, such as language, are distributed globally around the cerebrum.

Some of the support for this misconception has come from studies of split brains. A drastic way to deal with a rare and devastating neurological condition (intractable epilepsy) is to separate the two hemispheres of the brain. After sectioning the corpus callosum, a split-brained patient will have trouble producing verbal responses on the basis of sensory information processed on the right side of the cerebrum, leading to the idea that the left side is responsible for language function.

However, there are well-documented cases of language functions lost from damage to the right side of the brain. The deficits seen in damage to the left side of the brain are classified as aphasia, a loss of speech function; damage on the right side can affect the use of language. Right-side damage can result in a loss of ability to understand figurative aspects of speech, such as jokes, irony, or metaphors. Nonverbal aspects of speech can be affected by damage to the right side, such as facial expression or body language, and right-side damage can lead to a "flat affect" in speech, or a loss of emotional expression in speech—sounding like a robot when talking.

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to “through brain.” It is the connection between the cerebrum and the rest of the nervous system, with one exception. The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Output from the cerebrum passes through the diencephalon. The single exception is the system associated with **olfaction**, or the sense of smell, which connects directly with the cerebrum. In the earliest vertebrate species, the cerebrum was not much more than olfactory bulbs that received peripheral information about the chemical environment (to call it smell in these organisms is imprecise because they lived in the ocean).

The diencephalon is deep beneath the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with “thalamus” in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus ([link]). There are other structures, such as the **epithalamus**, which contains the pineal gland, or the **subthalamus**, which includes the subthalamic nucleus that is part of the

basal nuclei.

Thalamus

The **thalamus** is a collection of nuclei that relay information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. Axons from the peripheral sensory organs, or intermediate nuclei, synapse in the thalamus, and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction. The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention.

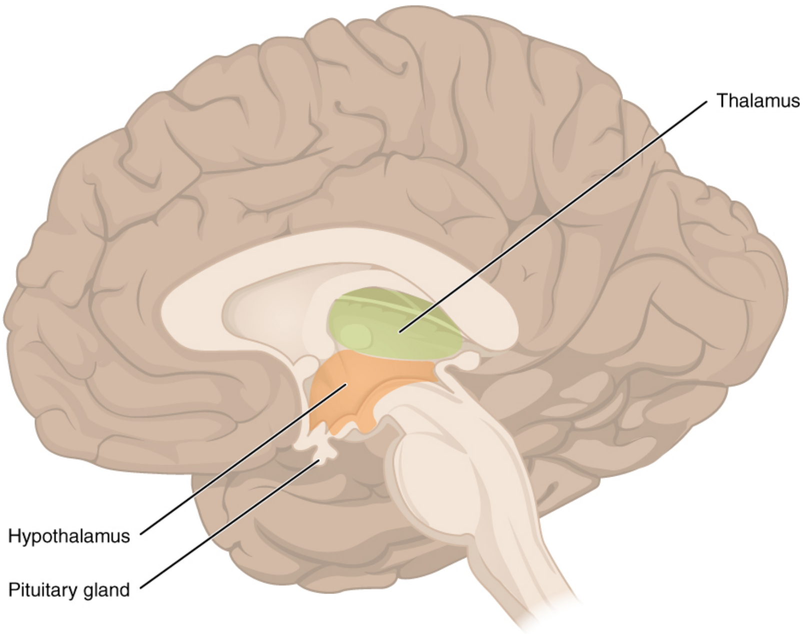
The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal nuclei, which involves connections with the thalamus. The primary output of the basal nuclei is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei.

Hypothalamus

Inferior and slightly anterior to the thalamus is the **hypothalamus**, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.

The Diencephalon

The diencephalon is composed primarily of the thalamus and hypothalamus, which together define the walls of the third ventricle. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.



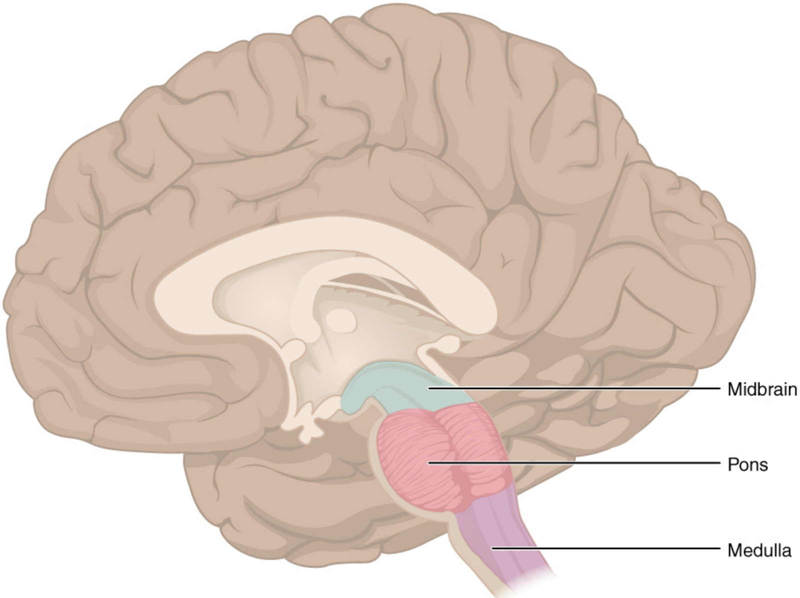
Brain Stem

The midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain stem ([link]). The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a separate region of the adult brain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates.

The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

The Brain Stem

The brain stem comprises three regions: the midbrain, the pons, and the medulla.



Midbrain

One of the original regions of the embryonic brain, the midbrain is a small region between the thalamus and pons. It is separated into the **tectum** and **tegmentum**, from the Latin words for roof and

floor, respectively. The cerebral aqueduct passes through the center of the midbrain, such that these regions are the roof and floor of that canal.

The tectum is composed of four bumps known as the colliculi (singular = colliculus), which means “little hill” in Latin. The **inferior colliculus** is the inferior pair of these enlargements and is part of the auditory brain stem pathway. Neurons of the inferior colliculus project to the thalamus, which then sends auditory information to the cerebrum for the conscious perception of sound. The **superior colliculus** is the superior pair and combines sensory information about visual space, auditory space, and somatosensory space. Activity in the superior colliculus is related to orienting the eyes to a sound or touch stimulus. If you are walking along the sidewalk on campus and you hear chirping, the superior colliculus coordinates that information with your awareness of the visual location of the tree right above you. That is the correlation of auditory and visual maps. If you suddenly feel something wet fall on your head, your superior colliculus integrates that with the auditory and visual maps and you know that the chirping bird just relieved itself on you. You want to look up to see the culprit, but do not.

The tegmentum is continuous with the gray matter of the rest of the brain stem. Throughout the midbrain, pons, and medulla, the tegmentum

contains the nuclei that receive and send information through the cranial nerves, as well as regions that regulate important functions such as those of the cardiovascular and respiratory systems.

Pons

The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. The bridge-like white matter is only the anterior surface of the pons; the gray matter beneath that is a continuation of the tegmentum from the midbrain. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the forebrain that is sent to the cerebellum.

Medulla

The medulla is the region known as the myelencephalon in the embryonic brain. The initial portion of the name, “myel,” refers to the significant white matter found in this region—especially on its exterior, which is continuous with the white matter of the spinal cord. The tegmentum of the midbrain and pons continues into the medulla because this gray matter is responsible for processing cranial nerve information. A diffuse region of gray matter

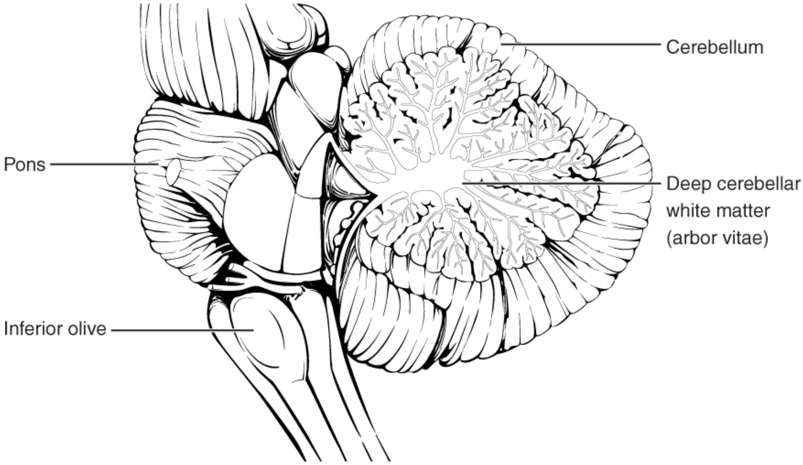
throughout the brain stem, known as the **reticular formation**, is related to sleep and wakefulness, such as general brain activity and attention.

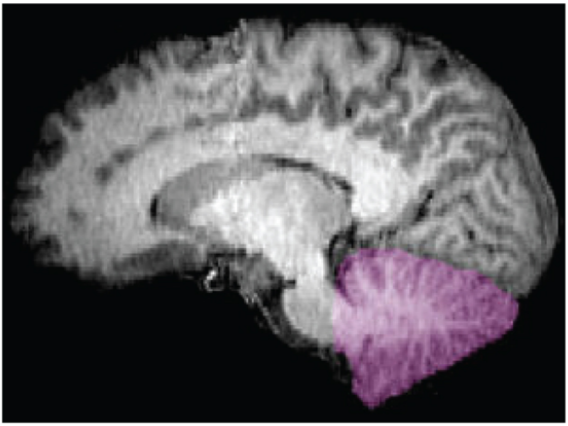
The Cerebellum

The **cerebellum**, as the name suggests, is the "little brain." It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain ([link]). The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.

The Cerebellum

The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.





Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the **inferior olive**. Fibers from this nucleus enter the cerebellum and

are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

The Spinal Cord

The description of the CNS is concentrated on the structures of the brain, but the spinal cord is another major organ of the system. Whereas the brain develops out of expansions of the neural tube into primary and then secondary vesicles, the spinal cord maintains the tube structure and is only specialized into certain regions. As the spinal cord continues to develop in the newborn, anatomical features mark its surface. The anterior midline is marked by the **anterior median fissure**, and the

posterior midline is marked by the **posterior median sulcus**. Axons enter the posterior side through the **dorsal (posterior) nerve root**, which marks the **posterolateral sulcus** on either side. The axons emerging from the anterior side do so through the **ventral (anterior) nerve root**. Note that it is common to see the terms dorsal (dorsal = “back”) and ventral (ventral = “belly”) used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. You should learn to be comfortable with both.

On the whole, the posterior regions are responsible for sensory functions and the anterior regions are associated with motor functions. This comes from the initial development of the spinal cord, which is divided into the **basal plate** and the **alar plate**. The basal plate is closest to the ventral midline of the neural tube, which will become the anterior face of the spinal cord and gives rise to motor neurons. The alar plate is on the dorsal side of the neural tube and gives rise to neurons that will receive sensory input from the periphery.

The length of the spinal cord is divided into regions that correspond to the regions of the vertebral column. The name of a spinal cord region corresponds to the level at which spinal nerves pass through the intervertebral foramina. Immediately adjacent to the brain stem is the cervical region,

followed by the thoracic, then the lumbar, and finally the sacral region. The spinal cord is not the full length of the vertebral column because the spinal cord does not grow significantly longer after the first or second year, but the skeleton continues to grow. The nerves that emerge from the spinal cord pass through the intervertebral formina at the respective levels. As the vertebral column grows, these nerves grow with it and result in a long bundle of nerves that resembles a horse's tail and is named the **cauda equina**. The sacral spinal cord is at the level of the upper lumbar vertebral bones. The spinal nerves extend from their various levels to the proper level of the vertebral column.

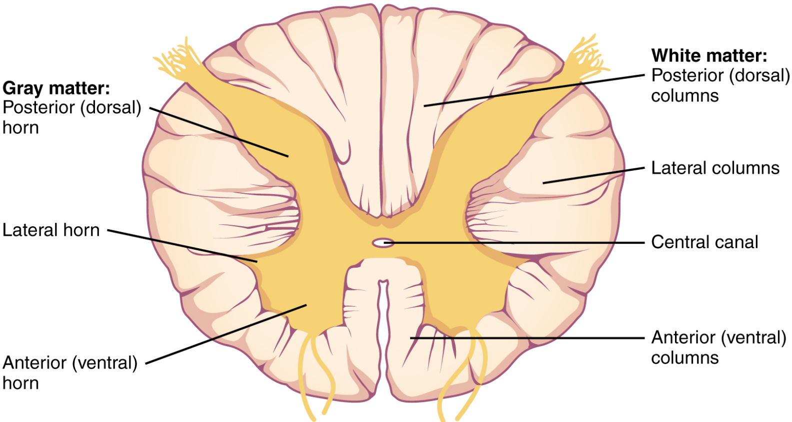
Gray Horns

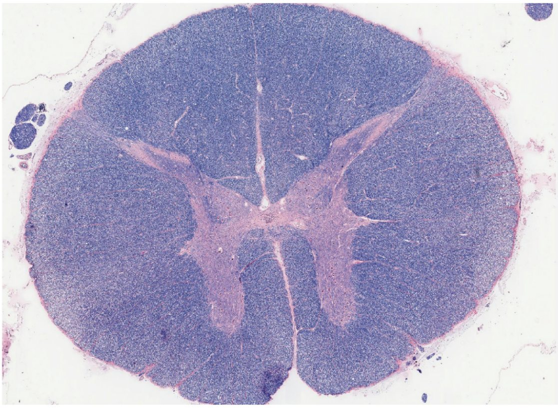
In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital "H." As shown in [link], the gray matter is subdivided into regions that are referred to as horns. The **posterior horn** is responsible for sensory processing. The **anterior horn** sends out motor signals to the skeletal muscles. The **lateral horn**, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system.

Some of the largest neurons of the spinal cord are the multipolar motor neurons in the anterior horn. The fibers that cause contraction of skeletal muscles are the axons of these neurons. The motor neuron that causes contraction of the big toe, for example, is located in the sacral spinal cord. The axon that has to reach all the way to the belly of that muscle may be a meter in length. The neuronal cell body that maintains that long fiber must be quite large, possibly several hundred micrometers in diameter, making it one of the largest cells in the body.

Cross-section of Spinal Cord

The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)





White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. **Ascending tracts** of nervous system fibers in these columns carry sensory information up to the brain, whereas **descending tracts** carry motor commands from the brain. Looking at the spinal cord longitudinally, the columns extend along its

length as continuous bands of white matter. Between the two posterior horns of gray matter are the **posterior columns**. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the **anterior columns**. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the **lateral columns**. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

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Watch this video to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections

represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

Disorders of the…

Basal Nuclei

Parkinson’s disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the effects of the direct and indirect pathways. Parkinson’s disease is the result of neurons in the substantia nigra pars compacta dying. These neurons release dopamine into the striatum. Without that modulatory influence, the basal nuclei are stuck in the indirect pathway, without the direct pathway being activated. The direct pathway is responsible for increasing cortical movement commands. The increased activity of the indirect pathway results in the hypokinetic disorder of Parkinson’s disease.

Parkinson’s disease is neurodegenerative, meaning that neurons die that cannot be replaced, so there is no cure for the disorder. Treatments for Parkinson’s disease are aimed at increasing dopamine levels in the striatum. Currently, the most common way of doing that is by providing the amino acid L-DOPA, which is a precursor to the

neurotransmitter dopamine and can cross the blood-brain barrier. With levels of the precursor elevated, the remaining cells of the substantia nigra pars compacta can make more neurotransmitter and have a greater effect. Unfortunately, the patient will become less responsive to L-DOPA treatment as time progresses, and it can cause increased dopamine levels elsewhere in the brain, which are associated with psychosis or schizophrenia.

Visit this site for a thorough explanation of Parkinson’s disease.

Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read this article in which the author explores the current understanding of why this happened.
According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?

Chapter Review

The adult brain is separated into four major regions: the cerebrum, the diencephalon, the brain stem, and

the cerebellum. The cerebrum is the largest portion and contains the cerebral cortex and subcortical nuclei. It is divided into two halves by the longitudinal fissure.

The cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for motor functions, from planning movements through executing commands to be sent to the spinal cord and periphery. The most anterior portion of the frontal lobe is the prefrontal cortex, which is associated with aspects of personality through its influence on motor responses in decision-making.

The other lobes are responsible for sensory functions. The parietal lobe is where somatosensation is processed. The occipital lobe is where visual processing begins, although the other parts of the brain can contribute to visual function. The temporal lobe contains the cortical area for auditory processing, but also has regions crucial for memory formation.

Nuclei beneath the cerebral cortex, known as the subcortical nuclei, are responsible for augmenting cortical functions. The basal nuclei receive input from cortical areas and compare it with the general state of the individual through the activity of a dopamine-releasing nucleus. The output influences the activity of part of the thalamus that can then

increase or decrease cortical activity that often results in changes to motor commands. The basal forebrain is responsible for modulating cortical activity in attention and memory. The limbic system includes deep cerebral nuclei that are responsible for emotion and memory.

The diencephalon includes the thalamus and the hypothalamus, along with some other structures. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates homeostatic functions through the autonomic and endocrine systems.

The brain stem is composed of the midbrain, pons, and medulla. It controls the head and neck region of the body through the cranial nerves. There are control centers in the brain stem that regulate the cardiovascular and respiratory systems.

The cerebellum is connected to the brain stem, primarily at the pons, where it receives a copy of the descending input from the cerebrum to the spinal cord. It can compare this with sensory feedback input through the medulla and send output through the midbrain that can correct motor commands for coordination.

Interactive Link Questions

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

Both cells are inhibitory. The first cell inhibits the second one. Therefore, the second cell can no longer inhibit its target. This is disinhibition of that target across two synapses.

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

By disinhibiting the subthalamic nucleus, the indirect pathway increases excitation of the globus pallidus internal segment. That, in turn, inhibits the thalamus, which is the opposite effect of the direct pathway that disinhibits the thalamus.

Watch this video to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

There are more motor neurons in the anterior horns that are responsible for movement in the limbs. The cervical enlargement is for the arms, and the lumbar enlargement is for the legs.

Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common

ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read this article in which the author explores the current understanding of why this happened.

According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?

Energy is needed for the brain to develop and perform higher cognitive functions. That energy is not available for the muscle tissues to develop and function. The hypothesis suggests that humans have larger brains and less muscle mass, and chimpanzees have the smaller brains but more muscle mass.

Review Questions

Which lobe of the cerebral cortex is responsible

for generating motor commands?

1. temporal
2. parietal
3. occipital
4. frontal

D

What region of the diencephalon coordinates homeostasis?

1. thalamus
2. epithalamus
3. hypothalamus
4. subthalamus

C

What level of the brain stem is the major input to the cerebellum?

1. midbrain
2. pons
3. medulla
4. spinal cord

B

What region of the spinal cord contains motor neurons that direct the movement of skeletal muscles?

1. anterior horn
2. posterior horn
3. lateral horn
4. alar plate

A

Brodmann’s areas map different regions of the ______ to particular functions.

1. cerebellum
2. cerebral cortex
3. basal forebrain
4. corpus callosum

B

Critical Thinking Questions

Damage to specific regions of the cerebral cortex, such as through a stroke, can result in specific losses of function. What functions would likely be lost by a stroke in the temporal lobe?

The temporal lobe has sensory functions associated with hearing and vision, as well as being important for memory. A stroke in the temporal lobe can result in specific sensory deficits in these systems (known as agnosias) or losses in memory.

Why do the anatomical inputs to the cerebellum suggest that it can compare motor commands and sensory feedback?

A copy of descending input from the cerebrum to the spinal cord, through the pons, and sensory feedback from the spinal cord and special senses like balance, through the medulla, both go to the cerebellum. It can therefore send output through the midbrain that will correct spinal cord control of skeletal muscle movements.

Glossary

alar plate
: developmental region of the spinal cord that gives rise to the posterior horn of the gray matter

amygdala
: nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior

anterior column
: white matter between the anterior horns of the spinal cord composed of many different groups of axons of both ascending and descending tracts

anterior horn
: gray matter of the spinal cord containing multipolar motor neurons, sometimes referred to as the ventral horn

anterior median fissure
: deep midline feature of the anterior spinal cord, marking the separation between the right and left sides of the cord

ascending tract
: central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain

basal forebrain

nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease

basal nuclei
: nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases

basal plate
: developmental region of the spinal cord that gives rise to the lateral and anterior horns of gray matter

Broca's area
: region of the frontal lobe associated with the motor commands necessary for speech production and located only in the cerebral hemisphere responsible for language production, which is the left side in approximately 95 percent of the population

Brodmann's areas
: mapping of regions of the cerebral cortex

based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s

cauda equina
: bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail

caudate
: nucleus deep in the cerebrum that is part of the basal nuclei; along with the putamen, it is part of the striatum

central sulcus
: surface landmark of the cerebral cortex that marks the boundary between the frontal and parietal lobes

cerebral cortex
: outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci

cerebrum
: region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion, and consciousness

cerebellum

region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord

cerebral hemisphere
: one half of the bilaterally symmetrical cerebrum

corpus callosum
: large white matter structure that connects the right and left cerebral hemispheres

descending tract
: central nervous system fibers carrying motor commands from the brain to the spinal cord or periphery

direct pathway
: connections within the basal nuclei from the striatum to the globus pallidus internal segment and substantia nigra pars reticulata that disinhibit the thalamus to increase cortical control of movement

disinhibition
: disynaptic connection in which the first synapse inhibits the second cell, which then stops inhibiting the final target

dorsal (posterior) nerve root
axons entering the posterior horn of the spinal cord

epithalamus
region of the diecephalon containing the pineal gland

frontal eye field
region of the frontal lobe associated with motor commands to orient the eyes toward an object of visual attention

frontal lobe
region of the cerebral cortex directly beneath the frontal bone of the cranium

globus pallidus
nuclei deep in the cerebrum that are part of the basal nuclei and can be divided into the internal and external segments

gyrus
ridge formed by convolutions on the surface of the cerebrum or cerebellum

hippocampus
gray matter deep in the temporal lobe that is very important for long-term memory formation

hypothalamus

major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

indirect pathway
: connections within the basal nuclei from the striatum through the globus pallidus external segment and subthalamic nucleus to the globus pallidus internal segment/substantia nigra pars compacta that result in inhibition of the thalamus to decrease cortical control of movement

inferior colliculus
: half of the midbrain tectum that is part of the brain stem auditory pathway

inferior olive
: nucleus in the medulla that is involved in processing information related to motor control

kinesthesia
: general sensory perception of movement of the body

lateral column
: white matter of the spinal cord between the posterior horn on one side and the axons from the anterior horn on the same side; composed of many different groups of axons, of both ascending and descending tracts, carrying

motor commands to and from the brain

lateral horn
: region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system

lateral sulcus
: surface landmark of the cerebral cortex that marks the boundary between the temporal lobe and the frontal and parietal lobes

limbic cortex
: collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system

limbic system
: structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation

longitudinal fissure
: large separation along the midline between the two cerebral hemispheres

occipital lobe
: region of the cerebral cortex directly beneath

the occipital bone of the cranium

olfaction
special sense responsible for smell, which has a unique, direct connection to the cerebrum

parietal lobe
region of the cerebral cortex directly beneath the parietal bone of the cranium

parieto-occipital sulcus
groove in the cerebral cortex representing the border between the parietal and occipital cortices

postcentral gyrus
primary motor cortex located in the frontal lobe of the cerebral cortex

posterior columns
white matter of the spinal cord that lies between the posterior horns of the gray matter, sometimes referred to as the dorsal column; composed of axons of ascending tracts that carry sensory information up to the brain

posterior horn
gray matter region of the spinal cord in which sensory input arrives, sometimes referred to as the dorsal horn

posterior median sulcus
: midline feature of the posterior spinal cord, marking the separation between right and left sides of the cord

posterolateral sulcus
: feature of the posterior spinal cord marking the entry of posterior nerve roots and the separation between the posterior and lateral columns of the white matter

precentral gyrus
: ridge just posterior to the central sulcus, in the parietal lobe, where somatosensory processing initially takes place in the cerebrum

prefrontal lobe
: specific region of the frontal lobe anterior to the more specific motor function areas, which can be related to the early planning of movements and intentions to the point of being personality-type functions

premotor area
: region of the frontal lobe responsible for planning movements that will be executed through the primary motor cortex

proprioception
: general sensory perceptions providing information about location and movement of

body parts; the “sense of the self”

putamen
: nucleus deep in the cerebrum that is part of the basal nuclei; along with the caudate, it is part of the striatum

reticular formation
: diffuse region of gray matter throughout the brain stem that regulates sleep, wakefulness, and states of consciousness

somatosensation
: general senses related to the body, usually thought of as the senses of touch, which would include pain, temperature, and proprioception

striatum
: the caudate and putamen collectively, as part of the basal nuclei, which receive input from the cerebral cortex

subcortical nucleus
: all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

substantia nigra pars compacta
: nuclei within the basal nuclei that release dopamine to modulate the function of the striatum; part of the motor pathway

substantia nigra pars reticulata
: nuclei within the basal nuclei that serve as an output center of the nuclei; part of the motor pathway

subthalamus
: nucleus within the basal nuclei that is part of the indirect pathway

sulcus
: groove formed by convolutions in the surface of the cerebral cortex

superior colliculus
: half of the midbrain tectum that is responsible for aligning visual, auditory, and somatosensory spatial perceptions

tectum
: region of the midbrain, thought of as the roof of the cerebral aqueduct, which is subdivided into the inferior and superior colliculi

tegmentum
: region of the midbrain, thought of as the floor of the cerebral aqueduct, which continues into the pons and medulla as the floor of the fourth ventricle

temporal lobe
: region of the cerebral cortex directly beneath the temporal bone of the cranium

thalamus

major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain, spinal cord, and periphery

ventral (anterior) nerve root

axons emerging from the anterior or lateral horns of the spinal cord

Introduction

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Fight or Flight?

Though the threats that modern humans face are not large predators, the autonomic nervous system is adapted to this type of stimulus. The modern world presents stimuli that trigger the same response. (credit: Vernon Swanepoel)

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the components of the autonomic nervous system
- Differentiate between the structures of the sympathetic and parasympathetic divisions in the autonomic nervous system
- Name the components of a visceral reflex

specific to the autonomic division to which it belongs
- Predict the response of a target effector to autonomic input on the basis of the released signaling molecule
- Describe how the central nervous system coordinates and contributes to autonomic functions

The autonomic nervous system is often associated with the “fight-or-flight response,” which refers to the preparation of the body to either run away from a threat or to stand and fight in the face of that threat. To suggest what this means, consider the (very unlikely) situation of seeing a lioness hunting out on the savannah. Though this is not a common threat that humans deal with in the modern world, it represents the type of environment in which the human species thrived and adapted. The spread of humans around the world to the present state of the modern age occurred much more quickly than any species would adapt to environmental pressures such as predators. However, the reactions modern humans have in the modern world are based on these prehistoric situations. If your boss is walking down the hallway on Friday afternoon looking for “volunteers” to come in on the weekend, your response is the same as the prehistoric human seeing the lioness running across the savannah: fight

or flight.

Most likely, your response to your boss—not to mention the lioness—would be flight. Run away! The autonomic system is responsible for the physiological response to make that possible, and hopefully successful. Adrenaline starts to flood your circulatory system. Your heart rate increases. Sweat glands become active. The bronchi of the lungs dilate to allow more air exchange. Pupils dilate to increase visual information. Blood pressure increases in general, and blood vessels dilate in skeletal muscles. Time to run. Similar physiological responses would occur in preparation for fighting off the threat.

This response should sound a bit familiar. The autonomic nervous system is tied into emotional responses as well, and the fight-or-flight response probably sounds like a panic attack. In the modern world, these sorts of reactions are associated with anxiety as much as with response to a threat. It is engrained in the nervous system to respond like this. In fact, the adaptations of the autonomic nervous system probably predate the human species and are likely to be common to all mammals, and perhaps shared by many animals. That lioness might herself be threatened in some other situation.

However, the autonomic nervous system is not just about responding to threats. Besides the fight-or-

flight response, there are the responses referred to as “rest and digest.” If that lioness is successful in her hunting, then she is going to rest from the exertion. Her heart rate will slow. Breathing will return to normal. The digestive system has a big job to do. Much of the function of the autonomic system is based on the connections within an autonomic, or visceral, reflex.

Autonomic Reflexes and Homeostasis
By the end of this section, you will be able to:

- Compare the structure of somatic and autonomic reflex arcs
- Explain the differences in sympathetic and parasympathetic reflexes
- Differentiate between short and long reflexes
- Determine the effect of the autonomic nervous system on the regulation of the various organ systems on the basis of the signaling molecules involved
- Describe the effects of drugs that affect autonomic function

The autonomic nervous system regulates organ systems through circuits that resemble the reflexes described in the somatic nervous system. The main difference between the somatic and autonomic systems is in what target tissues are effectors. Somatic responses are solely based on skeletal muscle contraction. The autonomic system, however, targets cardiac and smooth muscle, as well as glandular tissue. Whereas the basic circuit is a **reflex arc**, there are differences in the structure of those reflexes for the somatic and autonomic systems.

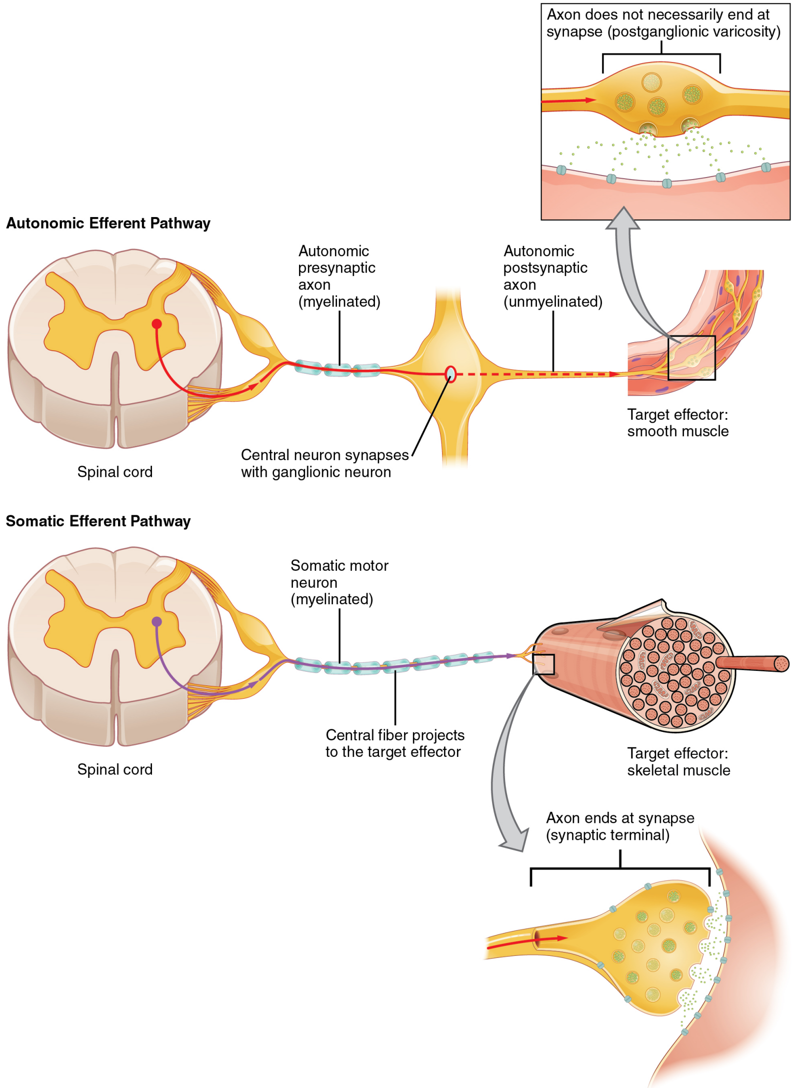
The Structure of Reflexes

One difference between a **somatic reflex**, such as the withdrawal reflex, and a **visceral reflex**, which is an autonomic reflex, is in the **efferent branch**. The output of a somatic reflex is the lower motor neuron in the ventral horn of the spinal cord that projects directly to a skeletal muscle to cause its contraction. The output of a visceral reflex is a two-step pathway starting with the preganglionic fiber emerging from a lateral horn neuron in the spinal cord, or a cranial nucleus neuron in the brain stem, to a ganglion—followed by the postganglionic fiber projecting to a target effector. The other part of a reflex, the **afferent branch**, is often the same between the two systems. Sensory neurons receiving input from the periphery—with cell bodies in the sensory ganglia, either of a cranial nerve or a dorsal root ganglion adjacent to the spinal cord—project into the CNS to initiate the reflex ([link]). The Latin root "effere" means "to carry." Adding the prefix "ef-" suggests the meaning "to carry away," whereas adding the prefix "af-" suggests "to carry toward or inward."

Comparison of Somatic and Visceral Reflexes

The afferent inputs to somatic and visceral reflexes are essentially the same, whereas the efferent branches are different. Somatic reflexes, for instance, involve a direct connection from the ventral horn of the spinal cord to the skeletal muscle. Visceral reflexes involve a projection from the central neuron to a ganglion, followed by a second projection from the ganglion to the target

effector.



Afferent Branch

The afferent branch of a reflex arc does differ between somatic and visceral reflexes in some

instances. Many of the inputs to visceral reflexes are from special or somatic senses, but particular senses are associated with the viscera that are not part of the conscious perception of the environment through the somatic nervous system. For example, there is a specific type of mechanoreceptor, called a **baroreceptor**, in the walls of the aorta and carotid sinuses that senses the stretch of those organs when blood volume or pressure increases. You do not have a conscious perception of having high blood pressure, but that is an important afferent branch of the cardiovascular and, particularly, vasomotor reflexes. The sensory neuron is essentially the same as any other general sensory neuron. The baroreceptor apparatus is part of the ending of a unipolar neuron that has a cell body in a sensory ganglion. The baroreceptors from the carotid arteries have axons in the glossopharyngeal nerve, and those from the aorta have axons in the vagus nerve.

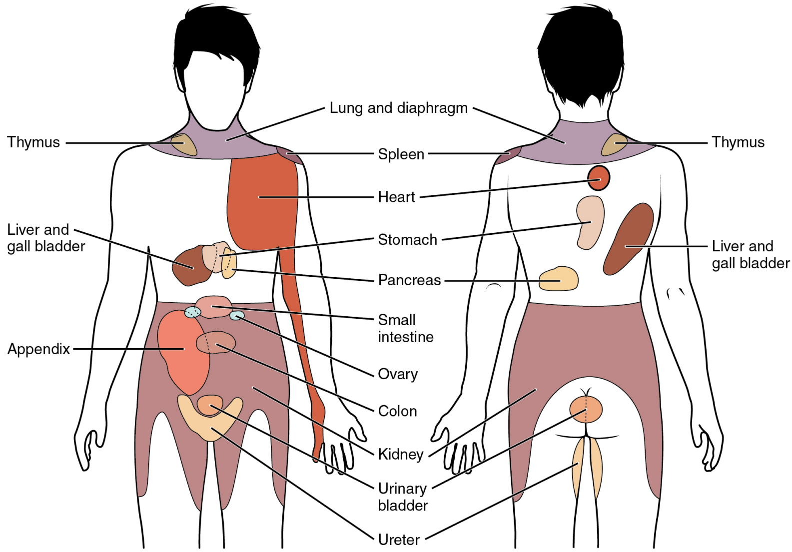
Though visceral senses are not primarily a part of conscious perception, those sensations sometimes make it to conscious awareness. If a visceral sense is strong enough, it will be perceived. The sensory homunculus—the representation of the body in the primary somatosensory cortex—only has a small region allotted for the perception of internal stimuli. If you swallow a large bolus of food, for instance, you will probably feel the lump of that food as it pushes through your esophagus, or even if your

stomach is distended after a large meal. If you inhale especially cold air, you can feel it as it enters your larynx and trachea. These sensations are not the same as feeling high blood pressure or blood sugar levels.

When particularly strong visceral sensations rise to the level of conscious perception, the sensations are often felt in unexpected places. For example, strong visceral sensations of the heart will be felt as pain in the left shoulder and left arm. This irregular pattern of projection of conscious perception of visceral sensations is called **referred pain**. Depending on the organ system affected, the referred pain will project to different areas of the body ([link]). The location of referred pain is not random, but a definitive explanation of the mechanism has not been established. The most broadly accepted theory for this phenomenon is that the visceral sensory fibers enter into the same level of the spinal cord as the somatosensory fibers of the referred pain location. By this explanation, the visceral sensory fibers from the mediastinal region, where the heart is located, would enter the spinal cord at the same level as the spinal nerves from the shoulder and arm, so the brain misinterprets the sensations from the mediastinal region as being from the axillary and brachial regions. Projections from the medial and inferior divisions of the cervical ganglia do enter the spinal cord at the middle to lower cervical levels, which is where the somatosensory fibers enter.

Referred Pain Chart

Conscious perception of visceral sensations map to specific regions of the body, as shown in this chart. Some sensations are felt locally, whereas others are perceived as affecting areas that are quite distant from the involved organ.



Disorders of the…

Nervous System: Kehr's Sign

Kehr's sign is the presentation of pain in the left shoulder, chest, and neck regions following rupture of the spleen. The spleen is in the upper-left abdominopelvic quadrant, but the pain is more in the shoulder and neck. How can this be? The sympathetic fibers connected to the spleen are from the celiac ganglion, which would be from the mid-thoracic to lower thoracic region whereas

parasympathetic fibers are found in the vagus nerve, which connects in the medulla of the brain stem. However, the neck and shoulder would connect to the spinal cord at the mid-cervical level of the spinal cord. These connections do not fit with the expected correspondence of visceral and somatosensory fibers entering at the same level of the spinal cord.

The incorrect assumption would be that the visceral sensations are coming from the spleen directly. In fact, the visceral fibers are coming from the diaphragm. The nerve connecting to the diaphragm takes a special route. The phrenic nerve is connected to the spinal cord at cervical levels 3 to 5. The motor fibers that make up this nerve are responsible for the muscle contractions that drive ventilation. These fibers have left the spinal cord to enter the phrenic nerve, meaning that spinal cord damage below the mid-cervical level is not fatal by making ventilation impossible. Therefore, the visceral fibers from the diaphragm enter the spinal cord at the same level as the somatosensory fibers from the neck and shoulder.

The diaphragm plays a role in Kehr’s sign because the spleen is just inferior to the diaphragm in the upper-left quadrant of the abdominopelvic cavity. When the spleen ruptures, blood spills into this region. The accumulating hemorrhage then puts pressure on the diaphragm. The visceral sensation is actually in the diaphragm, so the referred pain is in a region of the body that corresponds to the

diaphragm, not the spleen.

Efferent Branch

The efferent branch of the visceral reflex arc begins with the projection from the central neuron along the preganglionic fiber. This fiber then makes a synapse on the ganglionic neuron that projects to the target effector.

The effector organs that are the targets of the autonomic system range from the iris and ciliary body of the eye to the urinary bladder and reproductive organs. The thoracolumbar output, through the various sympathetic ganglia, reaches all of these organs. The cranial component of the parasympathetic system projects from the eye to part of the intestines. The sacral component picks up with the majority of the large intestine and the pelvic organs of the urinary and reproductive systems.

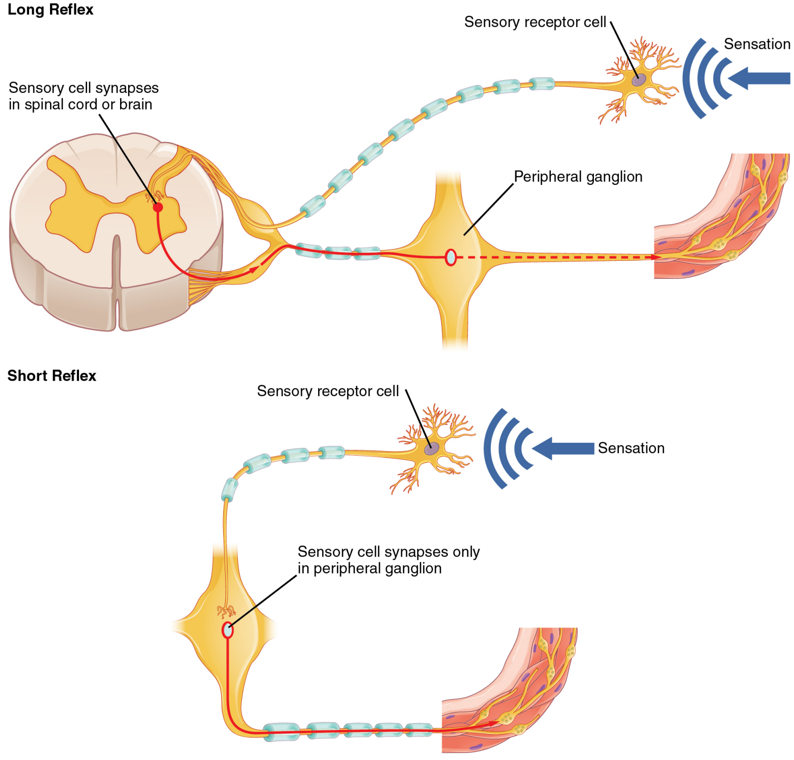
Short and Long Reflexes

Somatic reflexes involve sensory neurons that connect sensory receptors to the CNS and motor neurons that project back out to the skeletal muscles. Visceral reflexes that involve the thoracolumbar or craniosacral systems share similar

connections. However, there are reflexes that do not need to involve any CNS components. A **long reflex** has afferent branches that enter the spinal cord or brain and involve the efferent branches, as previously explained. A **short reflex** is completely peripheral and only involves the local integration of sensory input with motor output ([link]).

Short and Long Reflexes

Sensory input can stimulate either a short or a long reflex. A sensory neuron can project to the CNS or to an autonomic ganglion. The short reflex involves the direct stimulation of a postganglionic fiber by the sensory neuron, whereas the long reflex involves integration in the spinal cord or brain.



The difference between short and long reflexes is in the involvement of the CNS. Somatic reflexes always involve the CNS, even in a monosynaptic reflex in which the sensory neuron directly activates the motor neuron. That synapse is in the spinal cord or brain stem, so it has to involve the CNS. However, in the autonomic system there is the possibility that the CNS is not involved. Because the efferent branch of a visceral reflex involves two neurons—the central neuron and the ganglionic neuron—a “short circuit” can be possible. If a sensory neuron projects directly to the ganglionic neuron and causes it to activate the effector target, then the CNS is not involved.

A division of the nervous system that is related to the autonomic nervous system is the enteric nervous system. The word enteric refers to the digestive organs, so this represents the nervous tissue that is part of the digestive system. There are a few myenteric plexuses in which the nervous tissue in the wall of the digestive tract organs can directly influence digestive function. If stretch receptors in the stomach are activated by the filling and distension of the stomach, a short reflex will directly activate the smooth muscle fibers of the stomach wall to increase motility to digest the excessive food in the stomach. No CNS involvement is needed because the stretch receptor is directly activating a neuron in the wall of the stomach that causes the smooth muscle to contract. That neuron, connected

to the smooth muscle, is a postganglionic parasympathetic neuron that can be controlled by a fiber found in the vagus nerve.

Read this article to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

Balance in Competing Autonomic Reflex Arcs

The autonomic nervous system is important for

homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation). At the level of the target effector, the signal of which system is sending the message is strictly chemical. A signaling molecule binds to a receptor that causes changes in the target cell, which in turn causes the tissue or organ to respond to the changing conditions of the body.

Competing Neurotransmitters

The postganglionic fibers of the sympathetic and parasympathetic divisions both release neurotransmitters that bind to receptors on their targets. Postganglionic sympathetic fibers release norepinephrine, with a minor exception, whereas postganglionic parasympathetic fibers release ACh. For any given target, the difference in which division of the autonomic nervous system is exerting control is just in what chemical binds to its receptors. The target cells will have adrenergic and muscarinic receptors. If norepinephrine is released, it will bind to the adrenergic receptors present on the target cell, and if ACh is released, it will bind to the muscarinic receptors on the target cell.

In the sympathetic system, there are exceptions to this pattern of dual innervation. The postganglionic sympathetic fibers that contact the blood vessels

within skeletal muscle and that contact sweat glands do not release norepinephrine, they release ACh. This does not create any problem because there is no parasympathetic input to the sweat glands. Sweat glands have muscarinic receptors and produce and secrete sweat in response to the presence of ACh.

At most of the other targets of the autonomic system, the effector response is based on which neurotransmitter is released and what receptor is present. For example, regions of the heart that establish heart rate are contacted by postganglionic fibers from both systems. If norepinephrine is released onto those cells, it binds to an adrenergic receptor that causes the cells to depolarize faster, and the heart rate increases. If ACh is released onto those cells, it binds to a muscarinic receptor that causes the cells to hyperpolarize so that they cannot reach threshold as easily, and the heart rate slows. Without this parasympathetic input, the heart would work at a rate of approximately 100 beats per minute (bpm). The sympathetic system speeds that up, as it would during exercise, to 120–140 bpm, for example. The parasympathetic system slows it down to the resting heart rate of 60–80 bpm.

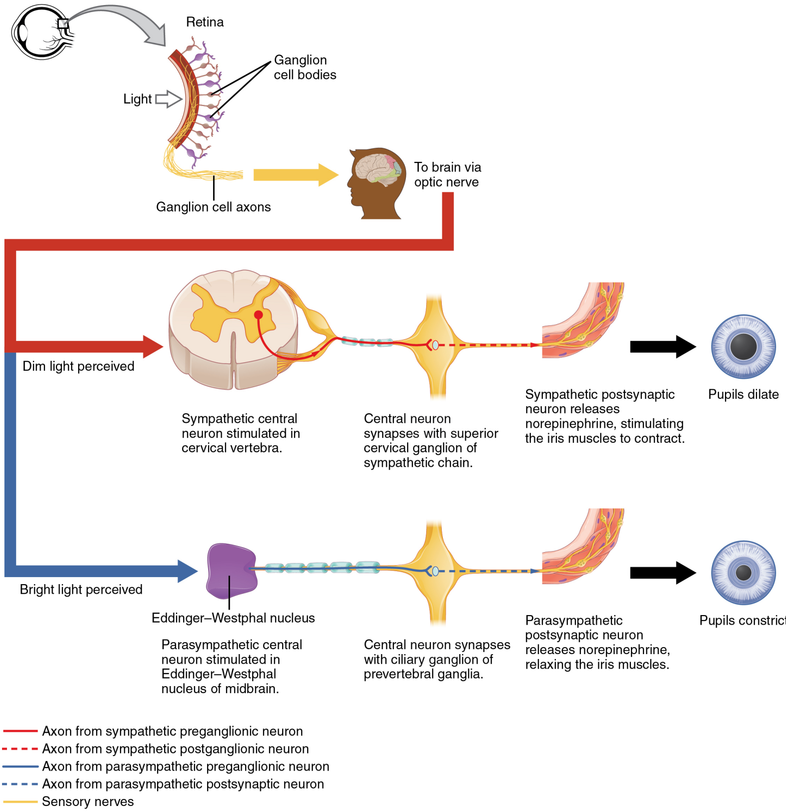
Another example is in the control of pupillary size ([link]). The afferent branch responds to light hitting the retina. Photoreceptors are activated, and the signal is transferred to the retinal ganglion cells that send an action potential along the optic nerve

into the diencephalon. If light levels are low, the sympathetic system sends a signal out through the upper thoracic spinal cord to the superior cervical ganglion of the sympathetic chain. The postganglionic fiber then projects to the iris, where it releases norepinephrine onto the radial fibers of the iris (a smooth muscle). When those fibers contract, the pupil dilates—increasing the amount of light hitting the retina. If light levels are too high, the parasympathetic system sends a signal out from the Eddinger–Westphal nucleus through the oculomotor nerve. This fiber synapses in the ciliary ganglion in the posterior orbit. The postganglionic fiber then projects to the iris, where it releases ACh onto the circular fibers of the iris—another smooth muscle. When those fibers contract, the pupil constricts to limit the amount of light hitting the retina.

Autonomic Control of Pupillary Size

Activation of the pupillary reflex comes from the amount of light activating the retinal ganglion cells, as sent along the optic nerve. The output of the sympathetic system projects through the superior cervical ganglion, whereas the parasympathetic system originates out of the midbrain and projects through the oculomotor nerve to the ciliary ganglion, which then projects to the iris. The postganglionic fibers of either division release neurotransmitters onto the smooth muscles of the iris to cause changes in the pupillary size. Norepinephrine results in dilation and ACh results

in constriction.



In this example, the autonomic system is controlling how much light hits the retina. It is a homeostatic reflex mechanism that keeps the activation of photoreceptors within certain limits. In the context of avoiding a threat like the lioness on the savannah, the sympathetic response for fight or flight will increase pupillary diameter so that more light hits the retina and more visual information is available for running away. Likewise, the parasympathetic response of rest reduces the amount of light reaching the retina, allowing the

photoreceptors to cycle through bleaching and be regenerated for further visual perception; this is what the homeostatic process is attempting to maintain.

Watch this video to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?

Autonomic Tone

Organ systems are balanced between the input from

the sympathetic and parasympathetic divisions. When something upsets that balance, the homeostatic mechanisms strive to return it to its regular state. For each organ system, there may be more of a sympathetic or parasympathetic tendency to the resting state, which is known as the **autonomic tone** of the system. For example, the heart rate was described above. Because the resting heart rate is the result of the parasympathetic system slowing the heart down from its intrinsic rate of 100 bpm, the heart can be said to be in parasympathetic tone.

In a similar fashion, another aspect of the cardiovascular system is primarily under sympathetic control. Blood pressure is partially determined by the contraction of smooth muscle in the walls of blood vessels. These tissues have adrenergic receptors that respond to the release of norepinephrine from postganglionic sympathetic fibers by constricting and increasing blood pressure. The hormones released from the adrenal medulla—epinephrine and norepinephrine—will also bind to these receptors. Those hormones travel through the bloodstream where they can easily interact with the receptors in the vessel walls. The parasympathetic system has no significant input to the systemic blood vessels, so the sympathetic system determines their tone.

There are a limited number of blood vessels that

respond to sympathetic input in a different fashion. Blood vessels in skeletal muscle, particularly those in the lower limbs, are more likely to dilate. It does not have an overall effect on blood pressure to alter the tone of the vessels, but rather allows for blood flow to increase for those skeletal muscles that will be active in the fight-or-flight response. The blood vessels that have a parasympathetic projection are limited to those in the erectile tissue of the reproductive organs. Acetylcholine released by these postganglionic parasympathetic fibers cause the vessels to dilate, leading to the engorgement of the erectile tissue.

Homeostatic Imbalances

Orthostatic Hypotension

Have you ever stood up quickly and felt dizzy for a moment? This is because, for one reason or another, blood is not getting to your brain so it is briefly deprived of oxygen. When you change position from sitting or lying down to standing, your cardiovascular system has to adjust for a new challenge, keeping blood pumping up into the head while gravity is pulling more and more blood down into the legs.

The reason for this is a sympathetic reflex that maintains the output of the heart in response to postural change. When a person stands up, proprioceptors indicate that the body is changing

position. A signal goes to the CNS, which then sends a signal to the upper thoracic spinal cord neurons of the sympathetic division. The sympathetic system then causes the heart to beat faster and the blood vessels to constrict. Both changes will make it possible for the cardiovascular system to maintain the rate of blood delivery to the brain. Blood is being pumped superiorly through the internal branch of the carotid arteries into the brain, against the force of gravity. Gravity is not increasing while standing, but blood is more likely to flow down into the legs as they are extended for standing. This sympathetic reflex keeps the brain well oxygenated so that cognitive and other neural processes are not interrupted.

Sometimes this does not work properly. If the sympathetic system cannot increase cardiac output, then blood pressure into the brain will decrease, and a brief neurological loss can be felt. This can be brief, as a slight "wooziness" when standing up too quickly, or a loss of balance and neurological impairment for a period of time. The name for this is orthostatic hypotension, which means that blood pressure goes below the homeostatic set point when standing. It can be the result of standing up faster than the reflex can occur, which may be referred to as a benign "head rush," or it may be the result of an underlying cause.

There are two basic reasons that orthostatic hypotension can occur. First, blood volume is too low and the sympathetic reflex is not effective. This

hypovolemia may be the result of dehydration or medications that affect fluid balance, such as diuretics or vasodilators. Both of these medications are meant to lower blood pressure, which may be necessary in the case of systemic hypertension, and regulation of the medications may alleviate the problem. Sometimes increasing fluid intake or water retention through salt intake can improve the situation.

The second underlying cause of orthostatic hypotension is autonomic failure. There are several disorders that result in compromised sympathetic functions. The disorders range from diabetes to multiple system atrophy (a loss of control over many systems in the body), and addressing the underlying condition can improve the hypotension. For example, with diabetes, peripheral nerve damage can occur, which would affect the postganglionic sympathetic fibers. Getting blood glucose levels under control can improve neurological deficits associated with diabetes.

Chapter Review

Autonomic nervous system function is based on the visceral reflex. This reflex is similar to the somatic reflex, but the efferent branch is composed of two

neurons. The central neuron projects from the spinal cord or brain stem to synapse on the ganglionic neuron that projects to the effector. The afferent branch of the somatic and visceral reflexes is very similar, as many somatic and special senses activate autonomic responses. However, there are visceral senses that do not form part of conscious perception. If a visceral sensation, such as cardiac pain, is strong enough, it will rise to the level of consciousness. However, the sensory homunculus does not provide a representation of the internal structures to the same degree as the surface of the body, so visceral sensations are often experienced as referred pain, such as feelings of pain in the left shoulder and arm in connection with a heart attack.

The role of visceral reflexes is to maintain a balance of function in the organ systems of the body. The two divisions of the autonomic system each play a role in effecting change, usually in competing directions. The sympathetic system increases heart rate, whereas the parasympathetic system decreases heart rate. The sympathetic system dilates the pupil of the eye, whereas the parasympathetic system constricts the pupil. The competing inputs can contribute to the resting tone of the organ system. Heart rate is normally under parasympathetic tone, whereas blood pressure is normally under sympathetic tone. The heart rate is slowed by the autonomic system at rest, whereas blood vessels retain a slight constriction at rest.

In a few systems of the body, the competing input from the two divisions is not the norm. The sympathetic tone of blood vessels is caused by the lack of parasympathetic input to the systemic circulatory system. Only certain regions receive parasympathetic input that relaxes the smooth muscle wall of the blood vessels. Sweat glands are another example, which only receive input from the sympathetic system.

Interactive Link Questions

Read this article to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

The effect of gravity on circulation means that it is harder to get blood up from the legs as the body takes on a vertical orientation.

Watch this video to learn about the pupillary

reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?

The optic nerve still carries the afferent input, but the output is from the thoracic spinal cord, through the superior cervical ganglion, to the radial fibers of the iris.

Review Questions

Which of the following represents a sensory input that is *not* part of both the somatic and autonomic systems?

1. vision
2. taste
3. baroreception
4. proprioception

C

What is the term for a reflex that does *not* include a CNS component?

1. long reflex
2. visceral reflex
3. somatic reflex
4. short reflex

D

What neurotransmitter will result in constriction of the pupil?

1. norepinephrine
2. acetylcholine
3. epinephrine
4. serotonin

B

What gland produces a secretion that causes fight-or-flight responses in effectors?

1. adrenal medulla
2. salivatory gland

3. reproductive gland
4. thymus

A

Which of the following is an incorrect pairing?

1. norepinephrine dilates the pupil
2. epinephrine increases blood pressure
3. acetylcholine decreases digestion
4. norepinephrine increases heart rate

C

Critical Thinking Questions

Damage to internal organs will present as pain associated with a particular surface area of the body. Why would something like irritation to the diaphragm, which is between the thoracic and abdominal cavities, feel like pain in the shoulder or neck?

The nerves that carry sensory information from the diaphragm enter the spinal cord in the

cervical region where somatic sensory fibers from the shoulder and neck would enter. The brain superimposes this experience onto the sensory homunculus where the somatic nerves are connected.

Medical practice is paying more attention to the autonomic system in considering disease states. Why would autonomic tone be important in considering cardiovascular disease?

Within the cardiovascular system, different aspects demonstrate variation in autonomic tone. Heart rate is under parasympathetic tone, and blood pressure is under sympathetic tone. Pharmaceuticals that treat cardiovascular disorders may be more effective if they work with the normal state of the autonomic system. Alternatively, some disorders may be exacerbated by autonomic deficits and common therapies might not be as effective.

Glossary

autonomic tone
: tendency of an organ system to be governed by one division of the autonomic nervous system over the other, such as heart rate being lowered by parasympathetic input at

rest

afferent branch
: component of a reflex arc that represents the input from a sensory neuron, for either a special or general sense

baroreceptor
: mechanoreceptor that senses the stretch of blood vessels to indicate changes in blood pressure

efferent branch
: component of a reflex arc that represents the output, with the target being an effector, such as muscle or glandular tissue

long reflex
: reflex arc that includes the central nervous system

referred pain
: the conscious perception of visceral sensation projected to a different region of the body, such as the left shoulder and arm pain as a sign for a heart attack

reflex arc
: circuit of a reflex that involves a sensory input and motor output, or an afferent branch and an efferent branch, and an integrating center to connect the two branches

short reflex

reflex arc that does not include any components of the central nervous system

somatic reflex

reflex involving skeletal muscle as the effector, under the control of the somatic nervous system

visceral reflex

reflex involving an internal organ as the effector, under the control of the autonomic nervous system

Central Control

By the end of this section, you will be able to:

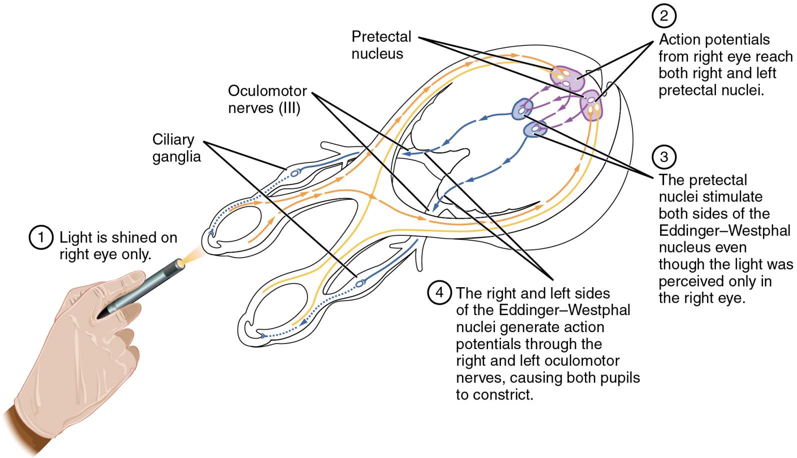
- Describe the role of higher centers of the brain in autonomic regulation
- Explain the connection of the hypothalamus to homeostasis
- Describe the regions of the CNS that link the autonomic system with emotion
- Describe the pathways important to descending control of the autonomic system

The pupillary light reflex ([link]) begins when light hits the retina and causes a signal to travel along the optic nerve. This is visual sensation, because the afferent branch of this reflex is simply sharing the special sense pathway. Bright light hitting the retina leads to the parasympathetic response, through the oculomotor nerve, followed by the postganglionic fiber from the ciliary ganglion, which stimulates the circular fibers of the iris to contract and constrict the pupil. When light hits the retina in one eye, both pupils contract. When that light is removed, both pupils dilate again back to the resting position. When the stimulus is unilateral (presented to only one eye), the response is bilateral (both eyes). The same is not true for somatic reflexes. If you touch a hot radiator, you only pull that arm back, not both. Central control of autonomic reflexes is different than for somatic reflexes. The hypothalamus, along with other CNS locations, controls the autonomic

system.

Pupillary Reflex Pathways

The pupil is under competing autonomic control in response to light levels hitting the retina. The sympathetic system will dilate the pupil when the retina is not receiving enough light, and the parasympathetic system will constrict the pupil when too much light hits the retina.



Forebrain Structures

Autonomic control is based on the visceral reflexes, composed of the afferent and efferent branches. These homeostatic mechanisms are based on the balance between the two divisions of the autonomic system, which results in tone for various organs that is based on the predominant input from the sympathetic or parasympathetic systems. Coordinating that balance requires integration that

begins with forebrain structures like the hypothalamus and continues into the brain stem and spinal cord.

The Hypothalamus

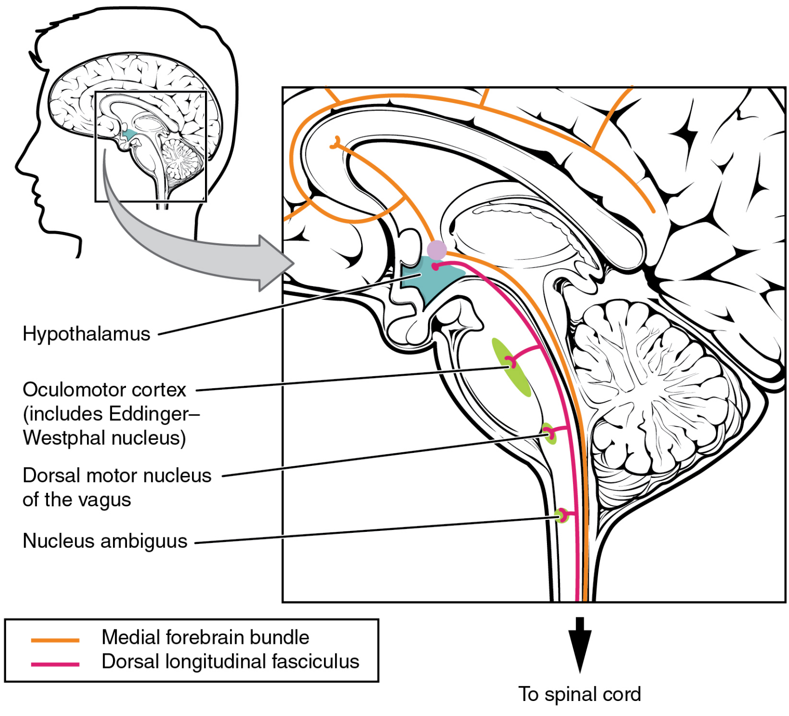
The hypothalamus is the control center for many homeostatic mechanisms. It regulates both autonomic function and endocrine function. The roles it plays in the pupillary reflexes demonstrates the importance of this control center. The optic nerve projects primarily to the thalamus, which is the necessary relay to the occipital cortex for conscious visual perception. Another projection of the optic nerve, however, goes to the hypothalamus.

The hypothalamus then uses this visual system input to drive the pupillary reflexes. If the retina is activated by high levels of light, the hypothalamus stimulates the parasympathetic response. If the optic nerve message shows that low levels of light are falling on the retina, the hypothalamus activates the sympathetic response. Output from the hypothalamus follows two main tracts, the **dorsal longitudinal fasciculus** and the **medial forebrain bundle** ([link]). Along these two tracts, the hypothalamus can influence the Eddinger–Westphal nucleus of the oculomotor complex or the lateral horns of the thoracic spinal cord.

Fiber Tracts of the Central Autonomic System

The hypothalamus is the source of most of the

central control of autonomic function. It receives input from cerebral structures and projects to brain stem and spinal cord structures to regulate the balance of sympathetic and parasympathetic input to the organ systems of the body. The main pathways for this are the medial forebrain bundle and the dorsal longitudinal fasciculus.



These two tracts connect the hypothalamus with the major parasympathetic nuclei in the brain stem and the preganglionic (central) neurons of the thoracolumbar spinal cord. The hypothalamus also receives input from other areas of the forebrain through the medial forebrain bundle. The olfactory cortex, the septal nuclei of the basal forebrain, and

the amygdala project into the hypothalamus through the medial forebrain bundle. These forebrain structures inform the hypothalamus about the state of the nervous system and can influence the regulatory processes of homeostasis. A good example of this is found in the amygdala, which is found beneath the cerebral cortex of the temporal lobe and plays a role in our ability to remember and feel emotions.

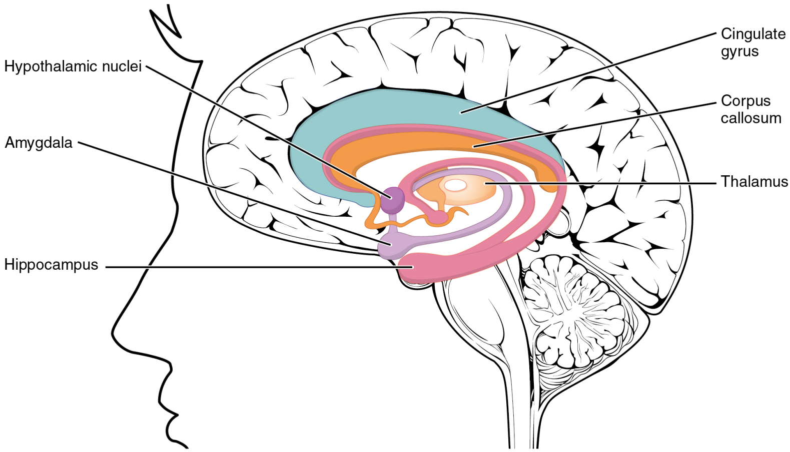
The Amygdala

The amygdala is a group of nuclei in the medial region of the temporal lobe that is part of the **limbic lobe** ([link]). The limbic lobe includes structures that are involved in emotional responses, as well as structures that contribute to memory function. The limbic lobe has strong connections with the hypothalamus and influences the state of its activity on the basis of emotional state. For example, when you are anxious or scared, the amygdala will send signals to the hypothalamus along the medial forebrain bundle that will stimulate the sympathetic fight-or-flight response. The hypothalamus will also stimulate the release of stress hormones through its control of the endocrine system in response to amygdala input.

The Limbic Lobe

Structures arranged around the edge of the cerebrum constitute the limbic lobe, which includes the amygdala, hippocampus, and cingulate gyrus,

and connects to the hypothalamus.



The Medulla

The medulla contains nuclei referred to as the **cardiovascular center**, which controls the smooth and cardiac muscle of the cardiovascular system through autonomic connections. When the homeostasis of the cardiovascular system shifts, such as when blood pressure changes, the coordination of the autonomic system can be accomplished within this region. Furthermore, when descending inputs from the hypothalamus stimulate this area, the sympathetic system can increase activity in the cardiovascular system, such as in response to anxiety or stress. The preganglionic sympathetic fibers that are responsible for increasing heart rate are referred to as the **cardiac accelerator nerves**, whereas the preganglionic sympathetic fibers responsible for constricting blood

vessels compose the **vasomotor nerves**.

Several brain stem nuclei are important for the visceral control of major organ systems. One brain stem nucleus involved in cardiovascular function is the solitary nucleus. It receives sensory input about blood pressure and cardiac function from the glossopharyngeal and vagus nerves, and its output will activate sympathetic stimulation of the heart or blood vessels through the upper thoracic lateral horn. Another brain stem nucleus important for visceral control is the dorsal motor nucleus of the vagus nerve, which is the motor nucleus for the parasympathetic functions ascribed to the vagus nerve, including decreasing the heart rate, relaxing bronchial tubes in the lungs, and activating digestive function through the enteric nervous system. The nucleus ambiguus, which is named for its ambiguous histology, also contributes to the parasympathetic output of the vagus nerve and targets muscles in the pharynx and larynx for swallowing and speech, as well as contributing to the parasympathetic tone of the heart along with the dorsal motor nucleus of the vagus.

Everyday Connections

Exercise and the Autonomic System

In addition to its association with the fight-or-flight response and rest-and-digest functions, the

autonomic system is responsible for certain everyday functions. For example, it comes into play when homeostatic mechanisms dynamically change, such as the physiological changes that accompany exercise. Getting on the treadmill and putting in a good workout will cause the heart rate to increase, breathing to be stronger and deeper, sweat glands to activate, and the digestive system to suspend activity. These are the same physiological changes associated with the fight-or-flight response, but there is nothing chasing you on that treadmill.

This is not a simple homeostatic mechanism at work because “maintaining the internal environment” would mean getting all those changes back to their set points. Instead, the sympathetic system has become active during exercise so that your body can cope with what is happening. A homeostatic mechanism is dealing with the conscious decision to push the body away from a resting state. The heart, actually, is moving away from its homeostatic set point. Without any input from the autonomic system, the heart would beat at approximately 100 bpm, and the parasympathetic system slows that down to the resting rate of approximately 70 bpm. But in the middle of a good workout, you should see your heart rate at 120–140 bpm. You could say that the body is stressed because of what you are doing to it. Homeostatic mechanisms are trying to keep blood pH in the normal range, or to keep body

temperature under control, but those are in response to the choice to exercise.

Watch this video to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body’s reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

Chapter Review

The autonomic system integrates sensory information and higher cognitive processes to generate output, which balances homeostatic mechanisms. The central autonomic structure is the hypothalamus, which coordinates sympathetic and parasympathetic efferent pathways to regulate activities of the organ systems of the body. The majority of hypothalamic output travels through the medial forebrain bundle and the dorsal longitudinal fasciculus to influence brain stem and spinal components of the autonomic nervous system. The medial forebrain bundle also connects the hypothalamus with higher centers of the limbic system where emotion can influence visceral responses. The amygdala is a structure within the limbic system that influences the hypothalamus in the regulation of the autonomic system, as well as the endocrine system.

These higher centers have descending control of the autonomic system through brain stem centers, primarily in the medulla, such as the cardiovascular center. This collection of medullary nuclei regulates cardiac function, as well as blood pressure. Sensory input from the heart, aorta, and carotid sinuses project to these regions of the medulla. The solitary nucleus increases sympathetic tone of the cardiovascular system through the cardiac accelerator and vasomotor nerves. The nucleus ambiguus and the dorsal motor nucleus both contribute fibers to the vagus nerve, which exerts

parasympathetic control of the heart by decreasing heart rate.

Interactive Link Questions

Watch this video to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body's reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

The release of urine in extreme fear. The sympathetic system normally constricts sphincters such as that of the urethra.

Review Questions

Which of these locations in the forebrain is the master control center for homeostasis through the autonomic and endocrine systems?

1. hypothalamus
2. thalamus
3. amygdala
4. cerebral cortex

A

Which nerve projects to the hypothalamus to indicate the level of light stimuli in the retina?

1. glossopharyngeal
2. oculomotor
3. optic
4. vagus

C

What region of the limbic lobe is responsible for generating stress responses via the hypothalamus?

1. hippocampus
2. amygdala
3. mammillary bodies

4. prefrontal cortex

B

What is another name for the preganglionic sympathetic fibers that project to the heart?

1. solitary tract
2. vasomotor nerve
3. vagus nerve
4. cardiac accelerator nerve

D

What central fiber tract connects forebrain and brain stem structures with the hypothalamus?

1. cardiac accelerator nerve
2. medial forebrain bundle
3. dorsal longitudinal fasciculus
4. corticospinal tract

B

Critical Thinking Questions

Horner's syndrome is a condition that presents with changes in one eye, such as pupillary constriction and dropping of eyelids, as well as decreased sweating in the face. Why could a tumor in the thoracic cavity have an effect on these autonomic functions?

Pupillary dilation and sweating, two functions lost in Horner's syndrome, are caused by the sympathetic system. A tumor in the thoracic cavity may interrupt the output of the thoracic ganglia that project to the head and face.

The cardiovascular center is responsible for regulating the heart and blood vessels through homeostatic mechanisms. What tone does each component of the cardiovascular system have? What connections does the cardiovascular center invoke to keep these two systems in their resting tone?

The heart—based on the resting heart rate—is under parasympathetic tone, and the blood vessels—based on the lack of parasympathetic input—are under sympathetic tone. The vagus nerve contributes to the lowered resting heart rate, whereas the vasomotor nerves maintain

the slight constriction of systemic blood vessels.

Glossary

cardiac accelerator nerves
: preganglionic sympathetic fibers that cause the heart rate to increase when the cardiovascular center in the medulla initiates a signal

cardiovascular center
: region in the medulla that controls the cardiovascular system through cardiac accelerator nerves and vasomotor nerves, which are components of the sympathetic division of the autonomic nervous system

dorsal longitudinal fasciculus
: major output pathway of the hypothalamus that descends through the gray matter of the brain stem and into the spinal cord

limbic lobe
: structures arranged around the edges of the cerebrum that are involved in memory and emotion

medial forebrain bundle
: fiber pathway that extends anteriorly into the basal forebrain, passes through the hypothalamus, and extends into the brain

stem and spinal cord

vasomotor nerves
: preganglionic sympathetic fibers that cause the constriction of blood vessels in response to signals from the cardiovascular center

Sensory Perception

By the end of this section, you will be able to:

- Describe different types of sensory receptors
- Describe the structures responsible for the special senses of taste, smell, hearing, balance, and vision
- Distinguish how different tastes are transduced
- Describe the means of mechanoreception for hearing and balance
- List the supporting structures around the eye and describe the structure of the eyeball
- Describe the processes of phototransduction

A major role of sensory receptors is to help us learn about the environment around us, or about the state of our internal environment. Stimuli from varying sources, and of different types, are received and changed into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response.

Describing sensory function with the term sensation or perception is a deliberate distinction. Sensation is

the activation of sensory receptor cells at the level of the stimulus. Perception is the central processing of sensory stimuli into a meaningful pattern. Perception is dependent on sensation, but not all sensations are perceived. Receptors are the cells or structures that detect sensations. A receptor cell is changed directly by a stimulus. A transmembrane protein receptor is a protein in the cell membrane that mediates a physiological change in a neuron, most often through the opening of ion channels or changes in the cell signaling processes. Transmembrane receptors are activated by chemicals called ligands. For example, a molecule in food can serve as a ligand for taste receptors. Other transmembrane proteins, which are not accurately called receptors, are sensitive to mechanical or thermal changes. Physical changes in these proteins increase ion flow across the membrane, and can generate an action potential or a graded potential in the sensory neurons.

Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type

and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the **transduction** of stimuli, or how the mechanical stimulus, light, or chemical changed the cell membrane potential.

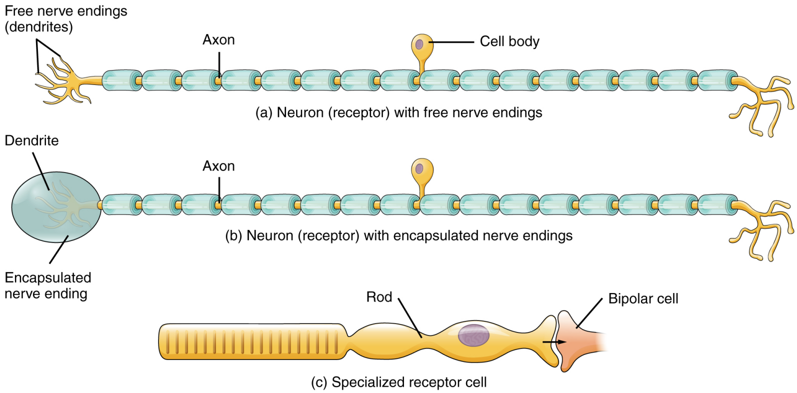
Structural Receptor Types

The cells that interpret information about the environment can be either (1) a neuron that has a **free nerve ending**, with dendrites embedded in tissue that would receive a sensation; (2) a neuron that has an **encapsulated ending** in which the sensory nerve endings are encapsulated in connective tissue that enhances their sensitivity; or (3) a specialized **receptor cell**, which has distinct structural components that interpret a specific type of stimulus ([link]). The pain and temperature receptors in the dermis of the skin are examples of neurons that have free nerve endings. Also located in the dermis of the skin are lamellated corpuscles, neurons with encapsulated nerve endings that respond to pressure and touch. The cells in the retina that respond to light stimuli are an example of a specialized receptor, a **photoreceptor**.

Receptor Classification by Cell Type

Receptor cell types can be classified on the basis of their structure. Sensory neurons can have either (a) free nerve endings or (b) encapsulated endings. Photoreceptors in the eyes, such as rod cells, are examples of (c) specialized receptor cells. These

cells release neurotransmitters onto a bipolar cell, which then synapses with the optic nerve neurons.



Another way that receptors can be classified is based on their location relative to the stimuli. An **exteroceptor** is a receptor that is located near a stimulus in the external environment, such as the somatosensory receptors that are located in the skin. An **interoceptor** is one that interprets stimuli from internal organs and tissues, such as the receptors that sense the increase in blood pressure in the aorta or carotid sinus. Finally, a **proprioceptor** is a receptor located near a moving part of the body, such as a muscle, that interprets the positions of the tissues as they move.

Functional Receptor Types

A third classification of receptors is by how the receptor transduces stimuli into membrane potential changes. Stimuli are of three general types. Some stimuli are ions and macromolecules that affect

transmembrane receptor proteins when these chemicals diffuse across the cell membrane. Some stimuli are physical variations in the environment that affect receptor cell membrane potentials. Other stimuli include the electromagnetic radiation from visible light. For humans, the only electromagnetic energy that is perceived by our eyes is visible light. Some other organisms have receptors that humans lack, such as the heat sensors of snakes, the ultraviolet light sensors of bees, or magnetic receptors in migratory birds.

Receptor cells can be further categorized on the basis of the type of stimuli they transduce. Chemical stimuli can be interpreted by a **chemoreceptor** that interprets chemical stimuli, such as an object's taste or smell. **Osmoreceptors** respond to solute concentrations of body fluids. Additionally, pain is primarily a chemical sense that interprets the presence of chemicals from tissue damage, or similar intense stimuli, through a **nociceptor**. Physical stimuli, such as pressure and vibration, as well as the sensation of sound and body position (balance), are interpreted through a **mechanoreceptor**. Another physical stimulus that has its own type of receptor is temperature, which is sensed through a **thermoreceptor** that is either sensitive to temperatures above (heat) or below (cold) normal body temperature.

Sensory Modalities

Ask anyone what the senses are, and they are likely to list the five major senses—taste, smell, touch, hearing, and sight. However, these are not all of the senses. The most obvious omission from this list is balance. Also, what is referred to simply as touch can be further subdivided into pressure, vibration, stretch, and hair-follicle position, on the basis of the type of mechanoreceptors that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors.

Within the realm of physiology, senses can be classified as either general or specific. A **general sense** is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to **proprioception** (body movement) and **kinesthesia** (body movement), or to a **visceral sense**, which is most important to autonomic functions. A **special sense** is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose.

Each of the senses is referred to as a **sensory modality**. Modality refers to the way that information is encoded, which is similar to the idea

of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors.

Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or **submodalities**, of the larger sense. An individual sensory modality represents the sensation of a specific type of stimulus. For example, the general sense of touch, which is known as **somatosensation**, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

Gustation (Taste)

Only a few recognized submodalities exist within the sense of taste, or **gustation**. Until recently, only four tastes were recognized: sweet, salty, sour, and bitter. Research at the turn of the 20th century led to recognition of the fifth taste, umami, during the mid-1980s. **Umami** is a Japanese word that means “delicious taste,” and is often translated to mean

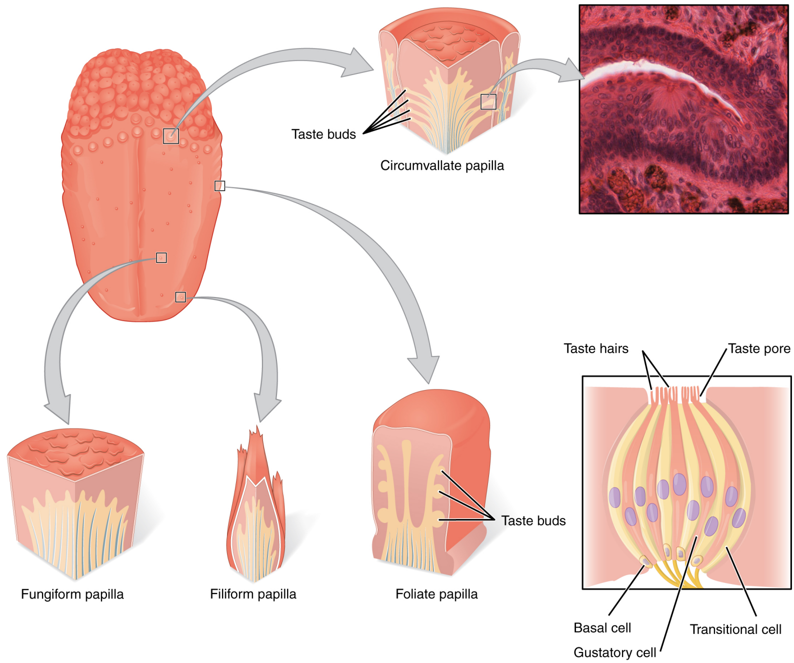
savory. Very recent research has suggested that there may also be a sixth taste for fats, or lipids.

Gustation is the special sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Raised bumps called **papillae** (singular = papilla) contain the structures for gustatory transduction. There are four types of papillae, based on their appearance ([link]): circumvallate, foliate, filiform, and fungiform. Within the structure of the papillae are **taste buds** that contain specialized **gustatory receptor cells** for the transduction of taste stimuli. These receptor cells are sensitive to the chemicals contained within foods that are ingested, and they release neurotransmitters based on the amount of the chemical in the food. Neurotransmitters from the gustatory cells can activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves.

The Tongue

The tongue is covered with small bumps, called papillae, which contain taste buds that are sensitive to chemicals in ingested food or drink. Different types of papillae are found in different regions of the tongue. The taste buds contain specialized gustatory receptor cells that respond to chemical stimuli dissolved in the saliva. These receptor cells activate sensory neurons that are part of the facial and glossopharyngeal nerves. LM × 1600. (Micrograph provided by the Regents of University

of Michigan Medical School © 2012)



Salty taste is simply the perception of sodium ions (Na+) in the saliva. When you eat something salty, the salt crystals dissociate into the component ions Na+ and Cl–, which dissolve into the saliva in your mouth. The Na+ concentration becomes high outside the gustatory cells, creating a strong concentration gradient that drives the diffusion of the ion into the cells. The entry of Na+ into these cells results in the depolarization of the cell membrane and the generation of a receptor potential.

Sour taste is the perception of H+ concentration. Just as with sodium ions in salty flavors, these

hydrogen ions enter the cell and trigger depolarization. Sour flavors are, essentially, the perception of acids in our food. Increasing hydrogen ion concentrations in the saliva (lowering saliva pH) triggers progressively stronger graded potentials in the gustatory cells. For example, orange juice—which contains citric acid—will taste sour because it has a pH value of approximately 3. Of course, it is often sweetened so that the sour taste is masked.

The first two tastes (salty and sour) are triggered by the cations Na^+ and H^+. The other tastes result from food molecules binding to a G protein–coupled receptor. A G protein signal transduction system ultimately leads to depolarization of the gustatory cell. The sweet taste is the sensitivity of gustatory cells to the presence of glucose dissolved in the saliva. Other monosaccharides such as fructose, or artificial sweeteners such as aspartame (NutraSweet™), saccharine, or sucralose (Splenda™) also activate the sweet receptors. The affinity for each of these molecules varies, and some will taste sweeter than glucose because they bind to the G protein–coupled receptor differently.

Bitter taste is similar to sweet in that food molecules bind to G protein–coupled receptors. However, there are a number of different ways in which this can happen because there are a large diversity of bitter-tasting molecules. Some bitter molecules depolarize gustatory cells, whereas others hyperpolarize

gustatory cells. Likewise, some bitter molecules increase G protein activation within the gustatory cells, whereas other bitter molecules decrease G protein activation. The specific response depends on which molecule is binding to the receptor.

One major group of bitter-tasting molecules are alkaloids. **Alkaloids** are nitrogen containing molecules that are commonly found in bitter-tasting plant products, such as coffee, hops (in beer), tannins (in wine), tea, and aspirin. By containing toxic alkaloids, the plant is less susceptible to microbe infection and less attractive to herbivores.

Therefore, the function of bitter taste may primarily be related to stimulating the gag reflex to avoid ingesting poisons. Because of this, many bitter foods that are normally ingested are often combined with a sweet component to make them more palatable (cream and sugar in coffee, for example). The highest concentration of bitter receptors appear to be in the posterior tongue, where a gag reflex could still spit out poisonous food.

The taste known as umami is often referred to as the savory taste. Like sweet and bitter, it is based on the activation of G protein–coupled receptors by a specific molecule. The molecule that activates this receptor is the amino acid L-glutamate. Therefore, the umami flavor is often perceived while eating protein-rich foods. Not surprisingly, dishes that

contain meat are often described as savory.

Once the gustatory cells are activated by the taste molecules, they release neurotransmitters onto the dendrites of sensory neurons. These neurons are part of the facial and glossopharyngeal cranial nerves, as well as a component within the vagus nerve dedicated to the gag reflex. The facial nerve connects to taste buds in the anterior third of the tongue. The glossopharyngeal nerve connects to taste buds in the posterior two thirds of the tongue. The vagus nerve connects to taste buds in the extreme posterior of the tongue, verging on the pharynx, which are more sensitive to noxious stimuli such as bitterness.

Watch this video to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, Pennsylvania, who became interested in science at an early age because of her sensory experiences. She recognized that her sense of taste was unique compared with other people she knew.

Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is able to visualize and count papillae on the surface of the tongue. People fall into two groups known as "tasters" and "non-tasters" based on the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?

Olfaction (Smell)

Like taste, the sense of smell, or **olfaction**, is also responsive to chemical stimuli. The olfactory receptor neurons are located in a small region within the superior nasal cavity ([link]). This region is referred to as the **olfactory epithelium** and contains bipolar sensory neurons. Each **olfactory sensory neuron** has dendrites that extend from the apical surface of the epithelium into the mucus lining the cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory

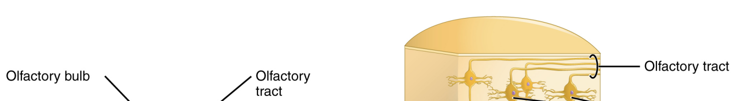
epithelial region and dissolve into the mucus. These **odorant molecules** bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory dendrites. The odorant–protein complex binds to a receptor protein within the cell membrane of an olfactory dendrite. These receptors are G protein–coupled, and will produce a graded membrane potential in the olfactory neurons.

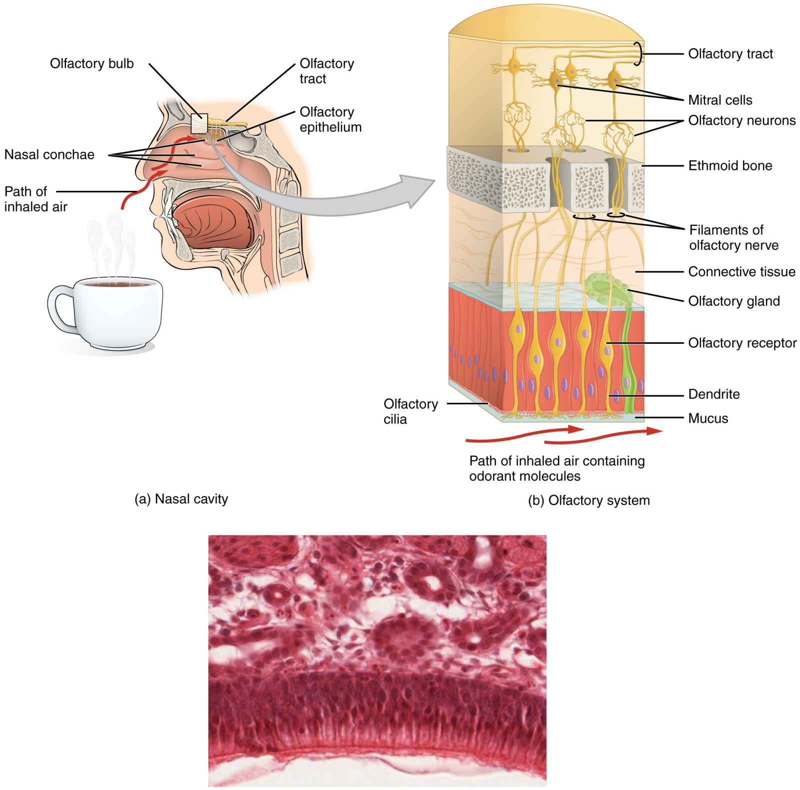
The axon of an olfactory neuron extends from the basal surface of the epithelium, through an olfactory foramen in the cribriform plate of the ethmoid bone, and into the brain. The group of axons called the olfactory tract connect to the **olfactory bulb** on the ventral surface of the frontal lobe. From there, the axons split to travel to several brain regions. Some travel to the cerebrum, specifically to the primary olfactory cortex that is located in the inferior and medial areas of the temporal lobe. Others project to structures within the limbic system and hypothalamus, where smells become associated with long-term memory and emotional responses. This is how certain smells trigger emotional memories, such as the smell of food associated with one’s birthplace. Smell is the one sensory modality that does not synapse in the thalamus before connecting to the cerebral cortex. This intimate connection between the olfactory system and the cerebral cortex is one reason why smell can be a potent trigger of memories and emotion.

The nasal epithelium, including the olfactory cells, can be harmed by airborne toxic chemicals. Therefore, the olfactory neurons are regularly replaced within the nasal epithelium, after which the axons of the new neurons must find their appropriate connections in the olfactory bulb. These new axons grow along the axons that are already in place in the cranial nerve.

The Olfactory System

(a) The olfactory system begins in the peripheral structures of the nasal cavity. (b) The olfactory receptor neurons are within the olfactory epithelium. (c) Axons of the olfactory receptor neurons project through the cribriform plate of the ethmoid bone and synapse with the neurons of the olfactory bulb (tissue source: simian). LM × 812. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)





(c) Olfactory epithelium

Disorders of the…

Olfactory System: Anosmia

Blunt force trauma to the face, such as that common in many car accidents, can lead to the loss of the olfactory nerve, and subsequently, loss of the sense of smell. This condition is known as **anosmia**. When the frontal lobe of the brain moves relative to the ethmoid bone, the olfactory tract axons may be sheared apart. Professional fighters often experience anosmia because of repeated

trauma to face and head. In addition, certain pharmaceuticals, such as antibiotics, can cause anosmia by killing all the olfactory neurons at once. If no axons are in place within the olfactory nerve, then the axons from newly formed olfactory neurons have no guide to lead them to their connections within the olfactory bulb. There are temporary causes of anosmia, as well, such as those caused by inflammatory responses related to respiratory infections or allergies.

Loss of the sense of smell can result in food tasting bland. A person with an impaired sense of smell may require additional spice and seasoning levels for food to be tasted. Anosmia may also be related to some presentations of mild depression, because the loss of enjoyment of food may lead to a general sense of despair.

The ability of olfactory neurons to replace themselves decreases with age, leading to age-related anosmia. This explains why some elderly people salt their food more than younger people do. However, this increased sodium intake can increase blood volume and blood pressure, increasing the risk of cardiovascular diseases in the elderly.

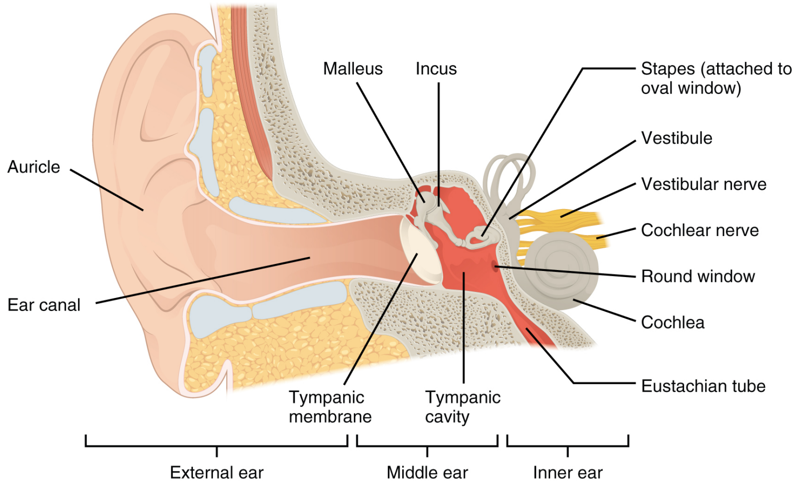
Audition (Hearing)

Hearing, or **audition**, is the transduction of sound

waves into a neural signal that is made possible by the structures of the ear ([link]). The large, fleshy structure on the lateral aspect of the head is known as the **auricle**. Some sources will also refer to this structure as the pinna, though that term is more appropriate for a structure that can be moved, such as the external ear of a cat. The C-shaped curves of the auricle direct sound waves toward the auditory canal. The canal enters the skull through the external auditory meatus of the temporal bone. At the end of the auditory canal is the **tympanic membrane**, or ear drum, which vibrates after it is struck by sound waves. The auricle, ear canal, and tympanic membrane are often referred to as the **external ear**. The **middle ear** consists of a space spanned by three small bones called the **ossicles**. The three ossicles are the **malleus**, **incus**, and **stapes**, which are Latin names that roughly translate to hammer, anvil, and stirrup. The malleus is attached to the tympanic membrane and articulates with the incus. The incus, in turn, articulates with the stapes. The stapes is then attached to the **inner ear**, where the sound waves will be transduced into a neural signal. The middle ear is connected to the pharynx through the Eustachian tube, which helps equilibrate air pressure across the tympanic membrane. The tube is normally closed but will pop open when the muscles of the pharynx contract during swallowing or yawning.

Structures of the Ear

The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively.



The inner ear is often described as a bony labyrinth, as it is composed of a series of canals embedded within the temporal bone. It has two separate regions, the **cochlea** and the **vestibule**, which are responsible for hearing and balance, respectively. The neural signals from these two regions are relayed to the brain stem through separate fiber bundles. However, these two distinct bundles travel together from the inner ear to the brain stem as the vestibulocochlear nerve. Sound is transduced into neural signals within the cochlear region of the inner ear, which contains the sensory neurons of the **spiral ganglia**. These ganglia are located within the

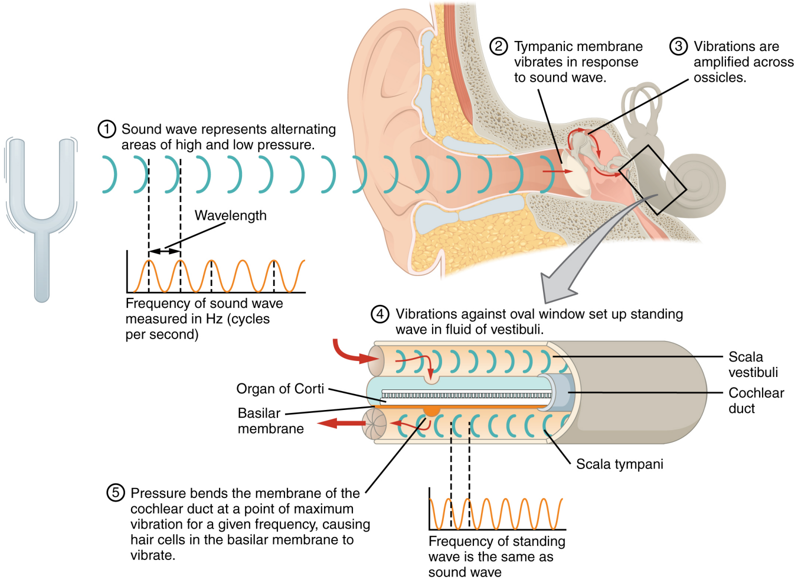
spiral-shaped cochlea of the inner ear. The cochlea is attached to the stapes through the **oval window**.

The oval window is located at the beginning of a fluid-filled tube within the cochlea called the **scala vestibuli**. The scala vestibuli extends from the oval window, travelling above the **cochlear duct**, which is the central cavity of the cochlea that contains the sound-transducing neurons. At the uppermost tip of the cochlea, the scala vestibuli curves over the top of the cochlear duct. The fluid-filled tube, now called the **scala tympani**, returns to the base of the cochlea, this time travelling under the cochlear duct. The scala tympani ends at the **round window**, which is covered by a membrane that contains the fluid within the scala. As vibrations of the ossicles travel through the oval window, the fluid of the scala vestibuli and scala tympani moves in a wave-like motion. The frequency of the fluid waves match the frequencies of the sound waves ([link]). The membrane covering the round window will bulge out or pucker in with the movement of the fluid within the scala tympani.

Transmission of Sound Waves to Cochlea

A sound wave causes the tympanic membrane to vibrate. This vibration is amplified as it moves across the malleus, incus, and stapes. The amplified vibration is picked up by the oval window causing pressure waves in the fluid of the scala vestibuli and scala tympani. The complexity of the pressure waves is determined by the changes in amplitude and

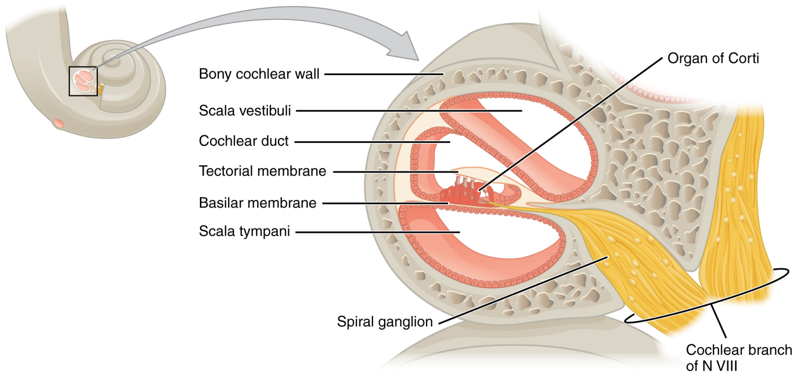
frequency of the sound waves entering the ear.



A cross-sectional view of the cochlea shows that the scala vestibuli and scala tympani run along both sides of the cochlear duct ([link]). The cochlear duct contains several **organs of Corti**, which tranduce the wave motion of the two scala into neural signals. The organs of Corti lie on top of the **basilar membrane**, which is the side of the cochlear duct located between the organs of Corti and the scala tympani. As the fluid waves move through the scala vestibuli and scala tympani, the basilar membrane moves at a specific spot, depending on the frequency of the waves. Higher frequency waves move the region of the basilar membrane that is close to the base of the cochlea. Lower frequency waves move the region of the basilar membrane that is near the tip of the cochlea.

Cross Section of the Cochlea

The three major spaces within the cochlea are highlighted. The scala tympani and scala vestibuli lie on either side of the cochlear duct. The organ of Corti, containing the mechanoreceptor hair cells, is adjacent to the scala tympani, where it sits atop the basilar membrane.

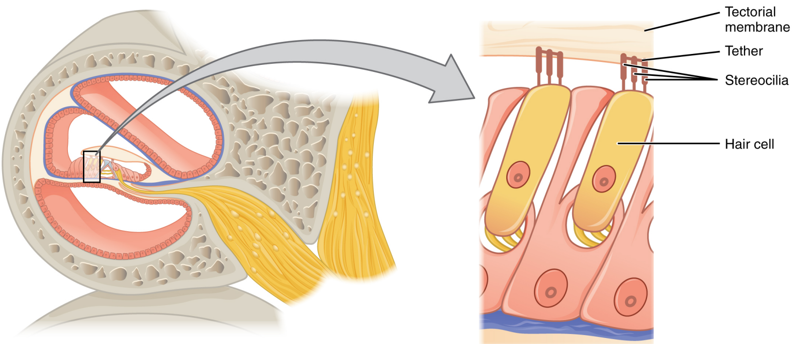


The organs of Corti contain **hair cells**, which are named for the hair-like **stereocilia** extending from the cell’s apical surfaces ([link]). The stereocilia are an array of microvilli-like structures arranged from tallest to shortest. Protein fibers tether adjacent hairs together within each array, such that the array will bend in response to movements of the basilar membrane. The stereocilia extend up from the hair cells to the overlying **tectorial membrane**, which is attached medially to the organ of Corti. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the tallest member of each array. When the stereocilia bend toward the tallest

member of their array, tension in the protein tethers opens ion channels in the hair cell membrane. This will depolarize the hair cell membrane, triggering nerve impulses that travel down the afferent nerve fibers attached to the hair cells. When the stereocilia bend toward the shortest member of their array, the tension on the tethers slackens and the ion channels close. When no sound is present, and the stereocilia are standing straight, a small amount of tension still exists on the tethers, keeping the membrane potential of the hair cell slightly depolarized.

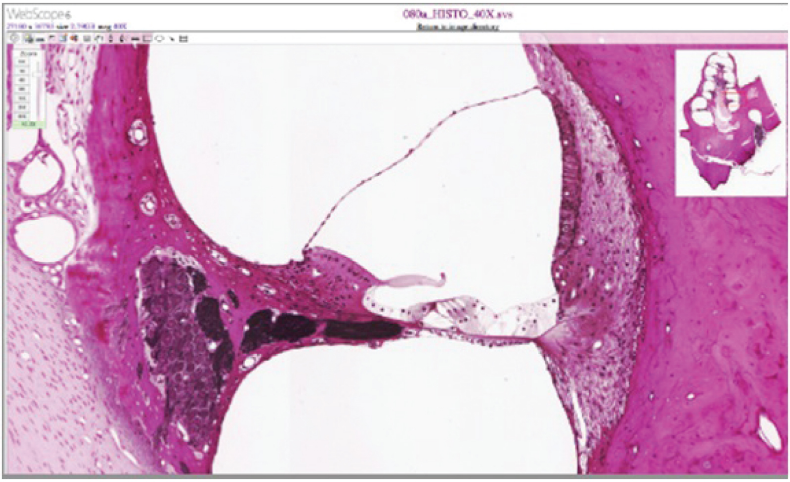
Hair Cell

The hair cell is a mechanoreceptor with an array of stereocilia emerging from its apical surface. The stereocilia are tethered together by proteins that open ion channels when the array is bent toward the tallest member of their array, and closed when the array is bent toward the shortest member of their array.



Cochlea and Organ of Corti

LM × 412. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



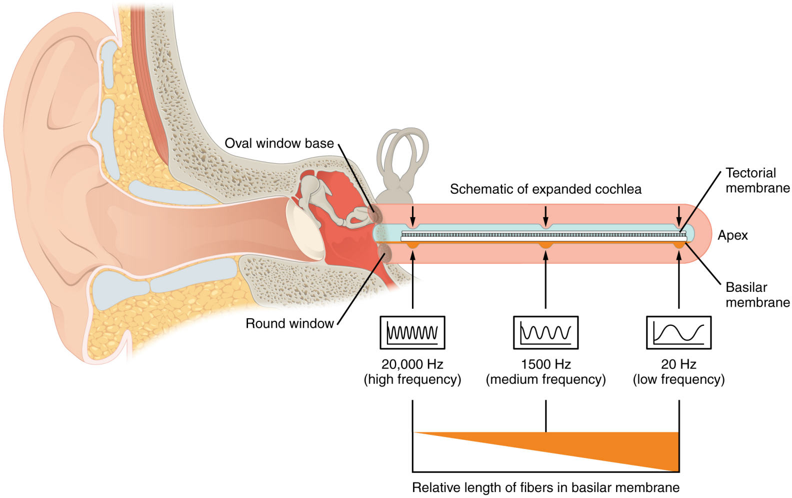
View the University of Michigan WebScope to explore the tissue sample in greater detail. The basilar membrane is the thin membrane that extends from the central core of the cochlea to the edge. What is anchored to this membrane so that they can be activated by movement of the fluids within the cochlea?

As stated above, a given region of the basilar membrane will only move if the incoming sound is at a specific frequency. Because the tectorial membrane only moves where the basilar membrane moves, the hair cells in this region will also only respond to sounds of this specific frequency. Therefore, as the frequency of a sound changes, different hair cells are activated all along the basilar membrane. The cochlea encodes auditory stimuli for frequencies between 20 and 20,000 Hz, which is the range of sound that human ears can detect. The unit of Hertz measures the frequency of sound waves in terms of cycles produced per second. Frequencies as low as 20 Hz are detected by hair cells at the apex, or tip, of the cochlea. Frequencies in the higher ranges of 20 KHz are encoded by hair cells at the base of the cochlea, close to the round and oval windows ([link]). Most auditory stimuli contain a mixture of sounds at a variety of frequencies and intensities (represented by the amplitude of the sound wave). The hair cells along the length of the cochlear duct, which are each sensitive to a particular frequency, allow the cochlea to separate auditory stimuli by frequency, just as a prism separates visible light into its component colors.

Frequency Coding in the Cochlea

The standing sound wave generated in the cochlea by the movement of the oval window deflects the basilar membrane on the basis of the frequency of sound. Therefore, hair cells at the base of the cochlea are activated only by high frequencies,

whereas those at the apex of the cochlea are activated only by low frequencies.



Watch this video to learn more about how the structures of the ear convert sound waves into a neural signal by moving the “hairs,” or stereocilia, of the cochlear duct. Specific locations along the length of the duct encode specific frequencies, or pitches. The brain interprets the meaning of the sounds we hear as music, speech, noise, etc. Which

ear structures are responsible for the amplification and transfer of sound from the external ear to the inner ear?

Watch this animation to learn more about the inner ear and to see the cochlea unroll, with the base at the back of the image and the apex at the front. Specific wavelengths of sound cause specific regions of the basilar membrane to vibrate, much like the keys of a piano produce sound at different frequencies. Based on the animation, where do frequencies—from high to low pitches—cause activity in the hair cells within the cochlear duct?

Equilibrium (Balance)

Along with audition, the inner ear is responsible for encoding information about **equilibrium**, the sense of balance. A similar mechanoreceptor—a hair cell

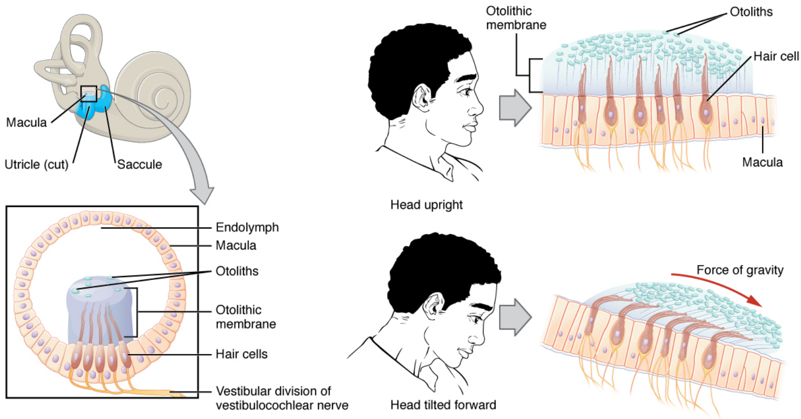
with stereocilia—senses head position, head movement, and whether our bodies are in motion. These cells are located within the vestibule of the inner ear. Head position is sensed by the **utricle** and **saccule**, whereas head movement is sensed by the **semicircular canals**. The neural signals generated in the **vestibular ganglion** are transmitted through the vestibulocochlear nerve to the brain stem and cerebellum.

The utricle and saccule are both largely composed of **macula** tissue (plural = maculae). The macula is composed of hair cells surrounded by support cells. The stereocilia of the hair cells extend into a viscous gel called the **otolithic membrane** ([link]). On top of the otolithic membrane is a layer of calcium carbonate crystals, called otoliths. The otoliths essentially make the otolithic membrane top-heavy. The otolithic membrane moves separately from the macula in response to head movements. Tilting the head causes the otolithic membrane to slide over the macula in the direction of gravity. The moving otolithic membrane, in turn, bends the sterocilia, causing some hair cells to depolarize as others hyperpolarize. The exact position of the head is interpreted by the brain based on the pattern of hair-cell depolarization.

Linear Acceleration Coding by Maculae

The maculae are specialized for sensing linear acceleration, such as when gravity acts on the tilting head, or if the head starts moving in a straight line.

The difference in inertia between the hair cell stereocilia and the otolithic membrane in which they are embedded leads to a shearing force that causes the stereocilia to bend in the direction of that linear acceleration.

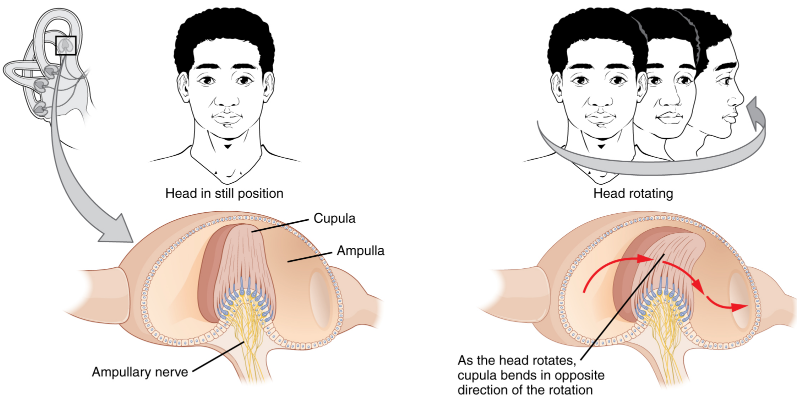


The semicircular canals are three ring-like extensions of the vestibule. One is oriented in the horizontal plane, whereas the other two are oriented in the vertical plane. The anterior and posterior vertical canals are oriented at approximately 45 degrees relative to the sagittal plane ([link]). The base of each semicircular canal, where it meets with the vestibule, connects to an enlarged region known as the **ampulla**. The ampulla contains the hair cells that respond to rotational movement, such as turning the head while saying "no." The stereocilia of these hair cells extend into the **cupula**, a membrane that attaches to the top of the ampulla. As the head rotates in a plane parallel to the semicircular canal, the fluid lags, deflecting the cupula in the direction opposite to the head

movement. The semicircular canals contain several ampullae, with some oriented horizontally and others oriented vertically. By comparing the relative movements of both the horizontal and vertical ampullae, the vestibular system can detect the direction of most head movements within three-dimensional (3-D) space.

Rotational Coding by Semicircular Canals

Rotational movement of the head is encoded by the hair cells in the base of the semicircular canals. As one of the canals moves in an arc with the head, the internal fluid moves in the opposite direction, causing the cupula and stereocilia to bend. The movement of two canals within a plane results in information about the direction in which the head is moving, and activation of all six canals can give a very precise indication of head movement in three dimensions.



Somatosensation (Touch)

Somatosensation is considered a general sense, as

opposed to the special senses discussed in this section. Somatosensation is the group of sensory modalities that are associated with touch, proprioception, and interoception. These modalities include pressure, vibration, light touch, tickle, itch, temperature, pain, proprioception, and kinesthesia. This means that its receptors are not associated with a specialized organ, but are instead spread throughout the body in a variety of organs. Many of the somatosensory receptors are located in the skin, but receptors are also found in muscles, tendons, joint capsules, ligaments, and in the walls of visceral organs.

Two types of somatosensory signals that are transduced by free nerve endings are pain and temperature. These two modalities use thermoreceptors and nociceptors to transduce temperature and pain stimuli, respectively. Temperature receptors are stimulated when local temperatures differ from body temperature. Some thermoreceptors are sensitive to just cold and others to just heat. Nociception is the sensation of potentially damaging stimuli. Mechanical, chemical, or thermal stimuli beyond a set threshold will elicit painful sensations. Stressed or damaged tissues release chemicals that activate receptor proteins in the nociceptors. For example, the sensation of heat associated with spicy foods involves **capsaicin**, the active molecule in hot peppers. Capsaicin molecules bind to a transmembrane ion channel in nociceptors

that is sensitive to temperatures above 37°C. The dynamics of capsaicin binding with this transmembrane ion channel is unusual in that the molecule remains bound for a long time. Because of this, it will decrease the ability of other stimuli to elicit pain sensations through the activated nociceptor. For this reason, capsaicin can be used as a topical analgesic, such as in products such as Icy Hot™.

If you drag your finger across a textured surface, the skin of your finger will vibrate. Such low frequency vibrations are sensed by mechanoreceptors called Merkel cells, also known as type I cutaneous mechanoreceptors. Merkel cells are located in the stratum basale of the epidermis. Deep pressure and vibration is transduced by lamellated (Pacinian) corpuscles, which are receptors with encapsulated endings found deep in the dermis, or subcutaneous tissue. Light touch is transduced by the encapsulated endings known as tactile (Meissner) corpuscles. Follicles are also wrapped in a plexus of nerve endings known as the hair follicle plexus. These nerve endings detect the movement of hair at the surface of the skin, such as when an insect may be walking along the skin. Stretching of the skin is transduced by stretch receptors known as bulbous corpuscles. Bulbous corpuscles are also known as Ruffini corpuscles, or type II cutaneous mechanoreceptors.

Other somatosensory receptors are found in the joints and muscles. Stretch receptors monitor the stretching of tendons, muscles, and the components of joints. For example, have you ever stretched your muscles before or after exercise and noticed that you can only stretch so far before your muscles spasm back to a less stretched state? This spasm is a reflex that is initiated by stretch receptors to avoid muscle tearing. Such stretch receptors can also prevent over-contraction of a muscle. In skeletal muscle tissue, these stretch receptors are called muscle spindles. Golgi tendon organs similarly transduce the stretch levels of tendons. Bulbous corpuscles are also present in joint capsules, where they measure stretch in the components of the skeletal system within the joint. The types of nerve endings, their locations, and the stimuli they transduce are presented in [link].

Mechanoreceptors of Somatosensation

Name	Historical (eponymous) name	Location(s)	Stimuli
Free nerve endings	*	Dermis, cornea,	Pain, temperature,

		tongue, joint capsules, visceral organs	mechanical deformation
Mechanoreceptors	Merkel's discs	Epidermal–dermal junction, mucosal membranes	Low frequency vibration (5–15 Hz)
Bulbous corpuscle	Ruffini's corpuscle	Dermis, joint capsules	Stretch
Tactile corpuscle	Meissner's corpuscle	Papillary dermis, especially in the fingertips and lips	Light touch, vibrations below 50 Hz
Lamellated corpuscle	Pacinian corpuscle	Deep dermis, subcutaneous tissue	Deep pressure, high-frequency vibration (around 250 Hz)
Hair follicle plexus	*	Wrapped around hair follicles in the dermis	Movement of hair
Muscle spindle	*	In line with skeletal muscle fibers	Muscle contraction and stretch

Tendon stretch organ	Golgi tendon organ	In line with tendons	Stretch of tendons

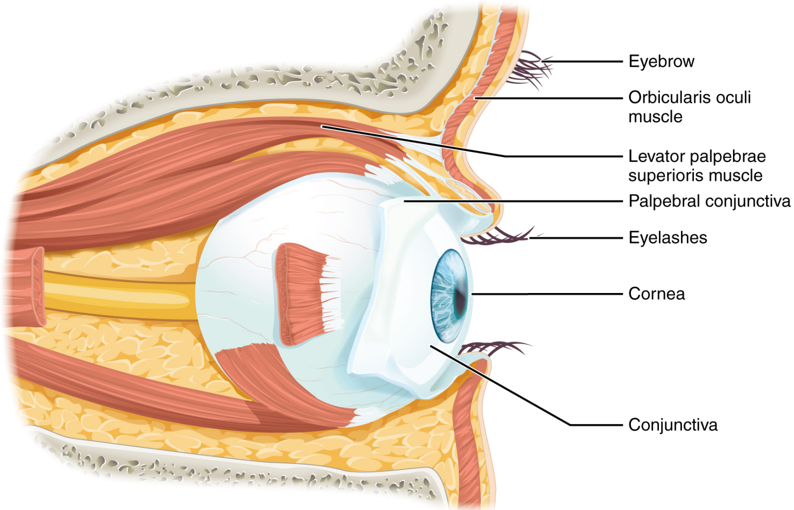
*No corresponding eponymous name.

Vision

Vision is the special sense of sight that is based on the transduction of light stimuli received through the eyes. The eyes are located within either orbit in the skull. The bony orbits surround the eyeballs, protecting them and anchoring the soft tissues of the eye ([link]). The eyelids, with lashes at their leading edges, help to protect the eye from abrasions by blocking particles that may land on the surface of the eye. The inner surface of each lid is a thin membrane known as the **palpebral conjunctiva**. The conjunctiva extends over the white areas of the eye (the sclera), connecting the eyelids to the eyeball. Tears are produced by the **lacrimal gland**, located beneath the lateral edges of the nose. Tears produced by this gland flow through the **lacrimal duct** to the medial corner of the eye, where the tears flow over the conjunctiva, washing away foreign particles.

The Eye in the Orbit

The eye is located within the orbit and surrounded by soft tissues that protect and support its function. The orbit is surrounded by cranial bones of the skull.



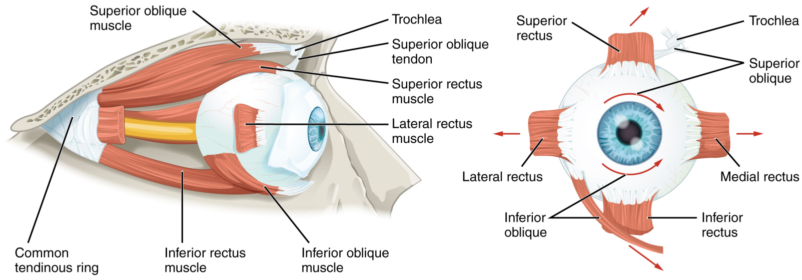
Movement of the eye within the orbit is accomplished by the contraction of six **extraocular muscles** that originate from the bones of the orbit and insert into the surface of the eyeball ([link]). Four of the muscles are arranged at the cardinal points around the eye and are named for those locations. They are the **superior rectus**, **medial rectus**, **inferior rectus**, and **lateral rectus**. When each of these muscles contract, the eye to moves toward the contracting muscle. For example, when the superior rectus contracts, the eye rotates to look up. The **superior oblique** originates at the posterior orbit, near the origin of the four rectus muscles. However, the tendon of the oblique muscles threads through a pulley-like piece of cartilage known as the **trochlea**. The tendon inserts obliquely into the superior surface of the eye. The angle of the tendon through the trochlea means that contraction of the superior oblique rotates the eye medially. The

inferior oblique muscle originates from the floor of the orbit and inserts into the inferolateral surface of the eye. When it contracts, it laterally rotates the eye, in opposition to the superior oblique. Rotation of the eye by the two oblique muscles is necessary because the eye is not perfectly aligned on the sagittal plane. When the eye looks up or down, the eye must also rotate slightly to compensate for the superior rectus pulling at approximately a 20-degree angle, rather than straight up. The same is true for the inferior rectus, which is compensated by contraction of the inferior oblique. A seventh muscle in the orbit is the **levator palpebrae superioris**, which is responsible for elevating and retracting the upper eyelid, a movement that usually occurs in concert with elevation of the eye by the superior rectus (see [link]).

The extraocular muscles are innervated by three cranial nerves. The lateral rectus, which causes abduction of the eye, is innervated by the abducens nerve. The superior oblique is innervated by the trochlear nerve. All of the other muscles are innervated by the oculomotor nerve, as is the levator palpebrae superioris. The motor nuclei of these cranial nerves connect to the brain stem, which coordinates eye movements.

Extraocular Muscles

The extraocular muscles move the eye within the orbit.



The eye itself is a hollow sphere composed of three layers of tissue. The outermost layer is the **fibrous tunic**, which includes the white **sclera** and clear **cornea**. The sclera accounts for five sixths of the surface of the eye, most of which is not visible, though humans are unique compared with many other species in having so much of the "white of the eye" visible ([link]). The transparent cornea covers the anterior tip of the eye and allows light to enter the eye. The middle layer of the eye is the **vascular tunic**, which is mostly composed of the choroid, ciliary body, and iris. The **choroid** is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the **ciliary body**, a muscular structure that is attached to the **lens** by suspensory ligaments, or **zonule fibers**. These two structures bend the lens, allowing it to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the **iris**—the colored part of the eye. The iris is a smooth muscle that opens or closes the **pupil**, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in

response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the **neural tunic**, or **retina**, which contains the nervous tissue responsible for photoreception.

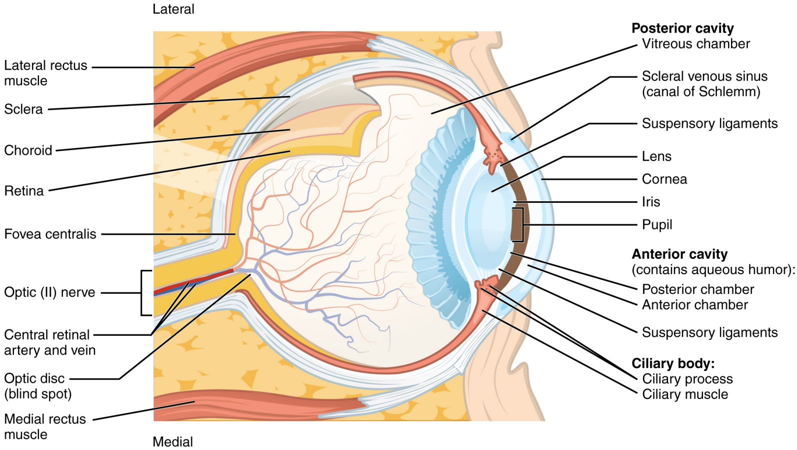
The eye is also divided into two cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the **aqueous humor**. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the **vitreous humor**.

The retina is composed of several layers and contains specialized cells for the initial processing of visual stimuli. The photoreceptors (rods and cones) change their membrane potential when stimulated by light energy. The change in membrane potential alters the amount of neurotransmitter that the photoreceptor cells release onto **bipolar cells** in the **outer synaptic layer**. It is the bipolar cell in the retina that connects a photoreceptor to a **retinal ganglion cell (RGC)** in the **inner synaptic layer**. There, **amacrine cells** additionally contribute to retinal processing before an action potential is produced by the RGC. The axons of RGCs, which lie at the innermost layer of the retina, collect at the **optic disc** and leave the eye as the **optic nerve** (see

[link]). Because these axons pass through the retina, there are no photoreceptors at the very back of the eye, where the optic nerve begins. This creates a "blind spot" in the retina, and a corresponding blind spot in our visual field.

Structure of the Eye

The sphere of the eye can be divided into anterior and posterior chambers. The wall of the eye is composed of three layers: the fibrous tunic, vascular tunic, and neural tunic. Within the neural tunic is the retina, with three layers of cells and two synaptic layers in between. The center of the retina has a small indentation known as the fovea.



Note that the photoreceptors in the retina (rods and cones) are located behind the axons, RGCs, bipolar cells, and retinal blood vessels. A significant amount of light is absorbed by these structures before the light reaches the photoreceptor cells. However, at the exact center of the retina is a small area known as the **fovea**. At the fovea, the retina lacks the

supporting cells and blood vessels, and only contains photoreceptors. Therefore, **visual acuity**, or the sharpness of vision, is greatest at the fovea. This is because the fovea is where the least amount of incoming light is absorbed by other retinal structures (see [link]). As one moves in either direction from this central point of the retina, visual acuity drops significantly. In addition, each photoreceptor cell of the fovea is connected to a single RGC. Therefore, this RGC does not have to integrate inputs from multiple photoreceptors, which reduces the accuracy of visual transduction. Toward the edges of the retina, several photoreceptors converge on RGCs (through the bipolar cells) up to a ratio of 50 to 1. The difference in visual acuity between the fovea and peripheral retina is easily evidenced by looking directly at a word in the middle of this paragraph. The visual stimulus in the middle of the field of view falls on the fovea and is in the sharpest focus. Without moving your eyes off that word, notice that words at the beginning or end of the paragraph are not in focus. The images in your peripheral vision are focused by the peripheral retina, and have vague, blurry edges and words that are not as clearly identified. As a result, a large part of the neural function of the eyes is concerned with moving the eyes and head so that important visual stimuli are centered on the fovea.

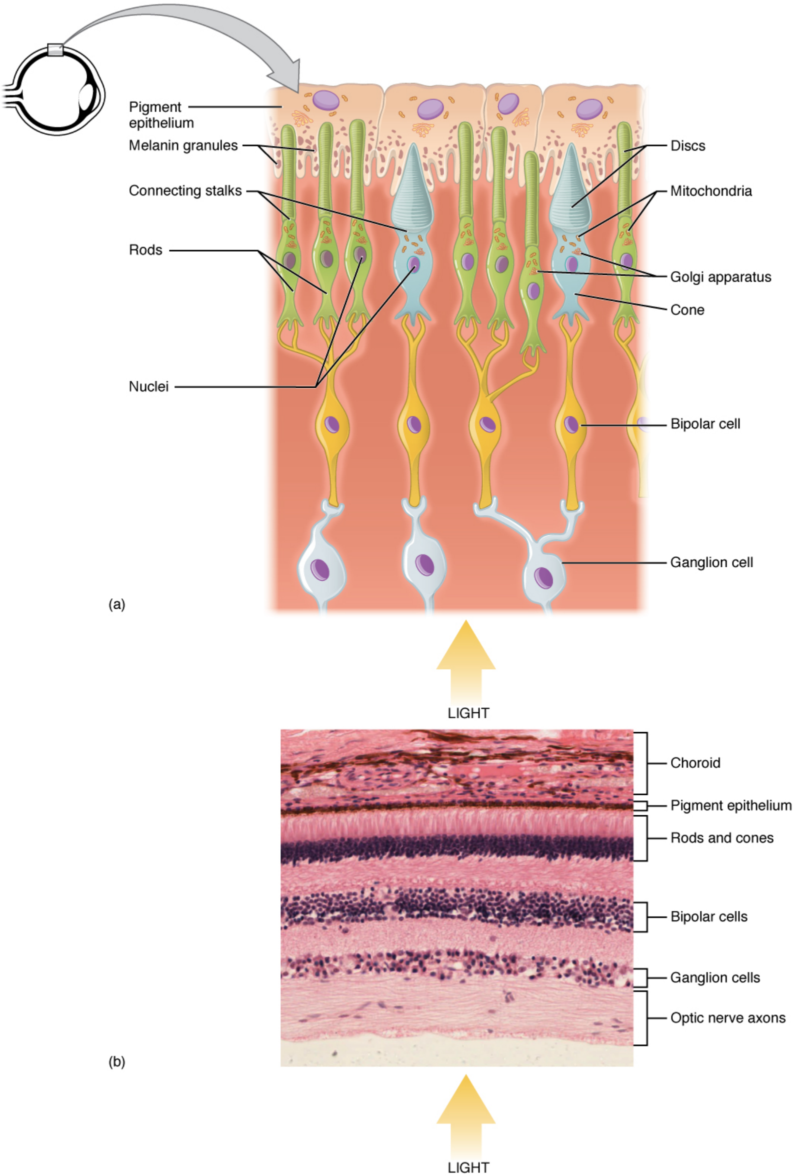
Light falling on the retina causes chemical changes

to pigment molecules in the photoreceptors, ultimately leading to a change in the activity of the RGCs. Photoreceptor cells have two parts, the **inner segment** and the **outer segment** ([link]). The inner segment contains the nucleus and other common organelles of a cell, whereas the outer segment is a specialized region in which photoreception takes place. There are two types of photoreceptors—rods and cones—which differ in the shape of their outer segment. The rod-shaped outer segments of the **rod photoreceptor** contain a stack of membrane-bound discs that contain the photosensitive pigment **rhodopsin**. The cone-shaped outer segments of the **cone photoreceptor** contain their photosensitive pigments in infoldings of the cell membrane. There are three cone photopigments, called **opsins**, which are each sensitive to a particular wavelength of light. The wavelength of visible light determines its color. The pigments in human eyes are specialized in perceiving three different primary colors: red, green, and blue.

Photoreceptor

(a) All photoreceptors have inner segments containing the nucleus and other important organelles and outer segments with membrane arrays containing the photosensitive opsin molecules. Rod outer segments are long columnar shapes with stacks of membrane-bound discs that contain the rhodopsin pigment. Cone outer segments are short, tapered shapes with folds of membrane in place of the discs in the rods. (b)

Tissue of the retina shows a dense layer of nuclei of the rods and cones. LM × 800. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



At the molecular level, visual stimuli cause changes in the photopigment molecule that lead to changes in membrane potential of the photoreceptor cell. A single unit of light is called a **photon**, which is described in physics as a packet of energy with properties of both a particle and a wave. The energy of a photon is represented by its wavelength, with each wavelength of visible light corresponding to a particular color. Visible light is electromagnetic radiation with a wavelength between 380 and 720 nm. Wavelengths of electromagnetic radiation longer than 720 nm fall into the infrared range, whereas wavelengths shorter than 380 nm fall into the ultraviolet range. Light with a wavelength of 380 nm is blue whereas light with a wavelength of 720 nm is dark red. All other colors fall between red and blue at various points along the wavelength scale.

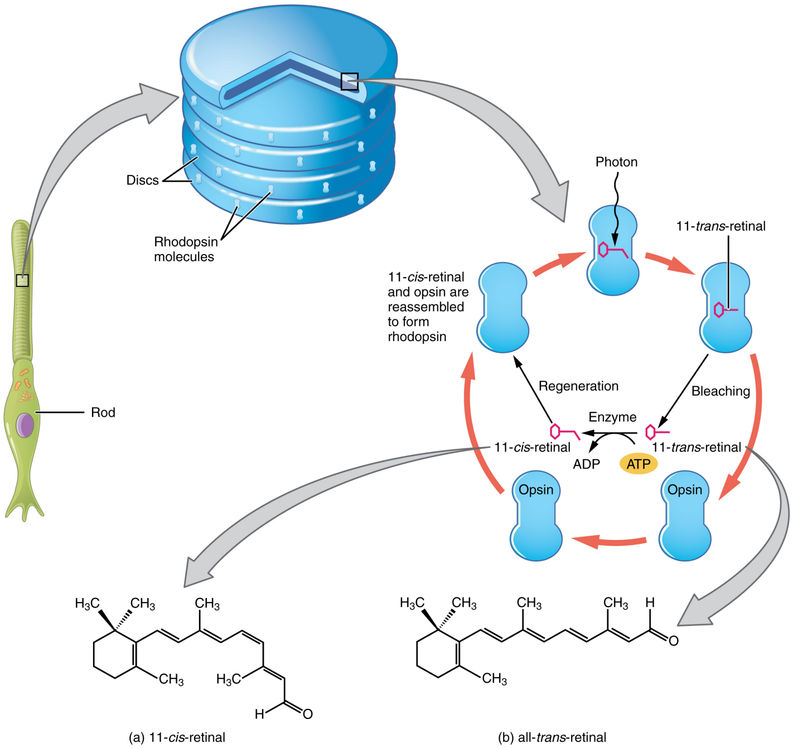
Opsin pigments are actually transmembrane proteins that contain a cofactor known as **retinal**. Retinal is a hydrocarbon molecule related to vitamin A. When a photon hits retinal, the long hydrocarbon chain of the molecule is biochemically altered. Specifically, photons cause some of the double-bonded carbons within the chain to switch from a *cis* to a *trans* conformation. This process is called **photoisomerization**. Before interacting with a photon, retinal's flexible double-bonded carbons are in the *cis* conformation. This molecule is referred to as 11-*cis*-retinal. A photon interacting with the

molecule causes the flexible double-bonded carbons to change to the *trans*- conformation, forming all-*trans*-retinal, which has a straight hydrocarbon chain ([link]).

The shape change of retinal in the photoreceptors initiates visual transduction in the retina. Activation of retinal and the opsin proteins result in activation of a G protein. The G protein changes the membrane potential of the photoreceptor cell, which then releases less neurotransmitter into the outer synaptic layer of the retina. Until the retinal molecule is changed back to the 11-*cis*-retinal shape, the opsin cannot respond to light energy, which is called bleaching. When a large group of photopigments is bleached, the retina will send information as if opposing visual information is being perceived. After a bright flash of light, afterimages are usually seen in negative. The photoisomerization is reversed by a series of enzymatic changes so that the retinal responds to more light energy.

Retinal Isomers

The retinal molecule has two isomers, (a) one before a photon interacts with it and (b) one that is altered through photoisomerization.



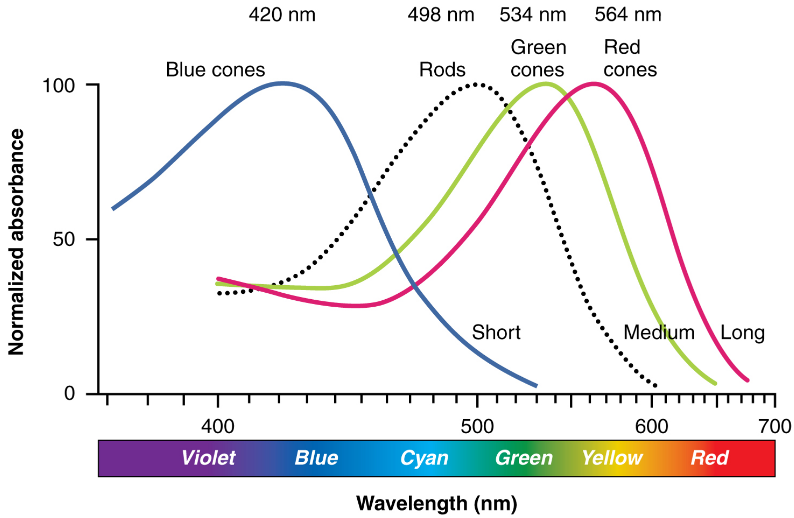
The opsins are sensitive to limited wavelengths of light. Rhodopsin, the photopigment in rods, is most sensitive to light at a wavelength of 498 nm. The three color opsins have peak sensitivities of 564 nm, 534 nm, and 420 nm corresponding roughly to the primary colors of red, green, and blue ([link]). The absorbance of rhodopsin in the rods is much more sensitive than in the cone opsins; specifically, rods are sensitive to vision in low light conditions, and cones are sensitive to brighter conditions. In normal sunlight, rhodopsin will be constantly bleached while the cones are active. In a darkened room, there is not enough light to activate cone opsins,

and vision is entirely dependent on rods. Rods are so sensitive to light that a single photon can result in an action potential from a rod's corresponding RGC.

The three types of cone opsins, being sensitive to different wavelengths of light, provide us with color vision. By comparing the activity of the three different cones, the brain can extract color information from visual stimuli. For example, a bright blue light that has a wavelength of approximately 450 nm would activate the "red" cones minimally, the "green" cones marginally, and the "blue" cones predominantly. The relative activation of the three different cones is calculated by the brain, which perceives the color as blue. However, cones cannot react to low-intensity light, and rods do not sense the color of light. Therefore, our low-light vision is—in essence—in grayscale. In other words, in a dark room, everything appears as a shade of gray. If you think that you can see colors in the dark, it is most likely because your brain knows what color something is and is relying on that memory.

Comparison of Color Sensitivity of Photopigments

Comparing the peak sensitivity and absorbance spectra of the four photopigments suggests that they are most sensitive to particular wavelengths.



Watch this video to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where “seeing,” or visual

perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that “specialized cells in the retina called ganglion cells convert the light rays into electrical signals.” What aspect of retinal processing is simplified by that statement? Explain your answer.

Sensory Nerves

Once any sensory cell transduces a stimulus into a nerve impulse, that impulse has to travel along axons to reach the CNS. In many of the special senses, the axons leaving the sensory receptors have a **topographical** arrangement, meaning that the location of the sensory receptor relates to the location of the axon in the nerve. For example, in the retina, axons from RGCs in the fovea are located at the center of the optic nerve, where they are surrounded by axons from the more peripheral RGCs.

Spinal Nerves

Generally, spinal nerves contain afferent axons from

sensory receptors in the periphery, such as from the skin, mixed with efferent axons travelling to the muscles or other effector organs. As the spinal nerve nears the spinal cord, it splits into dorsal and ventral roots. The dorsal root contains only the axons of sensory neurons, whereas the ventral roots contain only the axons of the motor neurons. Some of the branches will synapse with local neurons in the dorsal root ganglion, posterior (dorsal) horn, or even the anterior (ventral) horn, at the level of the spinal cord where they enter. Other branches will travel a short distance up or down the spine to interact with neurons at other levels of the spinal cord. A branch may also turn into the posterior (dorsal) column of the white matter to connect with the brain. For the sake of convenience, we will use the terms ventral and dorsal in reference to structures within the spinal cord that are part of these pathways. This will help to underscore the relationships between the different components. Typically, spinal nerve systems that connect to the brain are **contralateral**, in that the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain.

Cranial Nerves

Cranial nerves convey specific sensory information from the head and neck directly to the brain. For sensations below the neck, the right side of the body

is connected to the left side of the brain and the left side of the body to the right side of the brain. Whereas spinal information is contralateral, cranial nerve systems are mostly **ipsilateral**, meaning that a cranial nerve on the right side of the head is connected to the right side of the brain. Some cranial nerves contain only sensory axons, such as the olfactory, optic, and vestibulocochlear nerves. Other cranial nerves contain both sensory and motor axons, including the trigeminal, facial, glossopharyngeal, and vagus nerves (however, the vagus nerve is not associated with the somatic nervous system). The general senses of somatosensation for the face travel through the trigeminal system.

Chapter Review

The senses are olfaction (smell), gustation (taste), somatosensation (sensations associated with the skin and body), audition (hearing), equilibrium (balance), and vision. With the exception of somatosensation, this list represents the special senses, or those systems of the body that are associated with specific organs such as the tongue or eye. Somatosensation belongs to the general senses, which are those sensory structures that are distributed throughout the body and in the walls of various organs. The special senses are all primarily part of the somatic nervous system in that they are

consciously perceived through cerebral processes, though some special senses contribute to autonomic function. The general senses can be divided into somatosensation, which is commonly considered touch, but includes tactile, pressure, vibration, temperature, and pain perception. The general senses also include the visceral senses, which are separate from the somatic nervous system function in that they do not normally rise to the level of conscious perception.

The cells that transduce sensory stimuli into the electrochemical signals of the nervous system are classified on the basis of structural or functional aspects of the cells. The structural classifications are either based on the anatomy of the cell that is interacting with the stimulus (free nerve endings, encapsulated endings, or specialized receptor cell), or where the cell is located relative to the stimulus (interoceptor, exteroceptor, proprioceptor). Thirdly, the functional classification is based on how the cell transduces the stimulus into a neural signal. Chemoreceptors respond to chemical stimuli and are the basis for olfaction and gustation. Related to chemoreceptors are osmoreceptors and nociceptors for fluid balance and pain reception, respectively. Mechanoreceptors respond to mechanical stimuli and are the basis for most aspects of somatosensation, as well as being the basis of audition and equilibrium in the inner ear. Thermoreceptors are sensitive to temperature

changes, and photoreceptors are sensitive to light energy.

The nerves that convey sensory information from the periphery to the CNS are either spinal nerves, connected to the spinal cord, or cranial nerves, connected to the brain. Spinal nerves have mixed populations of fibers; some are motor fibers and some are sensory. The sensory fibers connect to the spinal cord through the dorsal root, which is attached to the dorsal root ganglion. Sensory information from the body that is conveyed through spinal nerves will project to the opposite side of the brain to be processed by the cerebral cortex. The cranial nerves can be strictly sensory fibers, such as the olfactory, optic, and vestibulocochlear nerves, or mixed sensory and motor nerves, such as the trigeminal, facial, glossopharyngeal, and vagus nerves. The cranial nerves are connected to the same side of the brain from which the sensory information originates.

Interactive Link Questions

Watch this video to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, PA, who became interested in science at an early age because of her sensory

experiences. She recognized that her sense of taste was unique compared with other people she knew. Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is able to visualize and count papillae on the surface of the tongue. People fall into two large groups known as "tasters" and "non-tasters" on the basis of the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?

Answers will vary, but a typical answer might be: I can eat most anything (except mushrooms!), so I don't think that I'm that sensitive to tastes. My whole family likes eating a variety of foods, so it seems that we all have the same level of sensitivity.

[link] The basilar membrane is the thin membrane that extends from the central core of

the cochlea to the edge. What is anchored to this membrane so that they can be activated by movement of the fluids within the cochlea?

[link] The hair cells are located in the organ of Corti, which is located on the basilar membrane. The stereocilia of those cells would normally be attached to the tectorial membrane (though they are detached in the micrograph because of processing of the tissue).

Watch this video to learn more about how the structures of the ear convert sound waves into a neural signal by moving the “hairs,” or stereocilia, of the cochlear duct. Specific locations along the length of the duct encode specific frequencies, or pitches. The brain interprets the meaning of the sounds we hear as music, speech, noise, etc. Which ear structures are responsible for the amplification and transfer of sound from the external ear to the inner ear?

The small bones in the middle ear, the ossicles, amplify and transfer sound between the tympanic membrane of the external ear and the oval window of the inner ear.

Watch this animation to learn more about the inner ear and to see the cochlea unroll, with the base at the back of the image and the apex at the front. Specific wavelengths of sound cause specific regions of the basilar membrane to vibrate, much like the keys of a piano produce sound at different frequencies. Based on the animation, where do frequencies—from high to low pitches—cause activity in the hair cells within the cochlear duct?

High frequencies activate hair cells toward the base of the cochlea, and low frequencies activate hair cells toward the apex of the cochlea.

Watch this video to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where “seeing,” or visual perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that

“specialized cells in the retina called ganglion cells convert the light rays into electrical signals.” What aspect of retinal processing is simplified by that statement? Explain your answer.

Photoreceptors convert light energy, or photons, into an electrochemical signal. The retina contains bipolar cells and the RGCs that finally convert it into action potentials that are sent from the retina to the CNS. It is important to recognize when popular media and online sources oversimplify complex physiological processes so that misunderstandings are not generated. This video was created by a medical device manufacturer who might be trying to highlight other aspects of the visual system than retinal processing. The statement they make is not incorrect, it just bundles together several steps, which makes it sound like RGCs are the transducers, rather than photoreceptors.

Review Questions

What type of receptor cell is responsible for transducing pain stimuli?

1. mechanoreceptor
2. nociceptor
3. osmoreceptor
4. photoreceptor

B

Which of these cranial nerves is part of the gustatory system?

1. olfactory
2. trochlear
3. trigeminal
4. facial

D

Which submodality of taste is sensitive to the pH of saliva?

1. umami
2. sour
3. bitter
4. sweet

B

Axons from which neuron in the retina make up the optic nerve?

1. amacrine cells
2. photoreceptors
3. bipolar cells
4. retinal ganglion cells

D

What type of receptor cell is involved in the sensations of sound and balance?

1. photoreceptor
2. chemoreceptor
3. mechanoreceptor
4. nociceptor

C

Critical Thinking Questions

The sweetener known as stevia can replace glucose in food. What does the molecular similarity of stevia to glucose mean for the

gustatory sense?

The stevia molecule is similar to glucose such that it will bind to the glucose receptor in sweet-sensitive taste buds. However, it is not a substrate for the ATP-generating metabolism within cells.

Why does the blind spot from the optic disc in either eye not result in a blind spot in the visual field?

The visual field for each eye is projected onto the retina as light is focused by the lens. The visual information from the right visual field falls on the left side of the retina and vice versa. The optic disc in the right eye is on the medial side of the fovea, which would be the left side of the retina. However, the optic disc in the left eye would be on the right side of that fovea, so the right visual field falls on the side of the retina in the left field where there is no blind spot.

Glossary

alkaloid
: substance, usually from a plant source, that is

chemically basic with respect to pH and will stimulate bitter receptors

amacrine cell
: type of cell in the retina that connects to the bipolar cells near the outer synaptic layer and provides the basis for early image processing within the retina

ampulla
: in the ear, the structure at the base of a semicircular canal that contains the hair cells and cupula for transduction of rotational movement of the head

anosmia
: loss of the sense of smell; usually the result of physical disruption of the first cranial nerve

aqueous humor
: watery fluid that fills the anterior chamber containing the cornea, iris, ciliary body, and lens of the eye

audition
: sense of hearing

auricle
: fleshy external structure of the ear

basilar membrane
: in the ear, the floor of the cochlear duct on

which the organ of Corti sits

bipolar cell
cell type in the retina that connects the photoreceptors to the RGCs

capsaicin
molecule that activates nociceptors by interacting with a temperature-sensitive ion channel and is the basis for “hot” sensations in spicy food

chemoreceptor
sensory receptor cell that is sensitive to chemical stimuli, such as in taste, smell, or pain

choroid
highly vascular tissue in the wall of the eye that supplies the outer retina with blood

ciliary body
smooth muscle structure on the interior surface of the iris that controls the shape of the lens through the zonule fibers

cochlea
auditory portion of the inner ear containing structures to transduce sound stimuli

cochlear duct
space within the auditory portion of the inner

ear that contains the organ of Corti and is adjacent to the scala tympani and scala vestibuli on either side

cone photoreceptor
: one of the two types of retinal receptor cell that is specialized for color vision through the use of three photopigments distributed through three separate populations of cells

contralateral
: word meaning “on the opposite side,” as in axons that cross the midline in a fiber tract

cornea
: fibrous covering of the anterior region of the eye that is transparent so that light can pass through it

cupula
: specialized structure within the base of a semicircular canal that bends the stereocilia of hair cells when the head rotates by way of the relative movement of the enclosed fluid

encapsulated ending
: configuration of a sensory receptor neuron with dendrites surrounded by specialized structures to aid in transduction of a particular type of sensation, such as the lamellated corpuscles in the deep dermis and subcutaneous tissue

equilibrium
: sense of balance that includes sensations of position and movement of the head

external ear
: structures on the lateral surface of the head, including the auricle and the ear canal back to the tympanic membrane

exteroceptor
: sensory receptor that is positioned to interpret stimuli from the external environment, such as photoreceptors in the eye or somatosensory receptors in the skin

extraocular muscle
: one of six muscles originating out of the bones of the orbit and inserting into the surface of the eye which are responsible for moving the eye

fibrous tunic
: outer layer of the eye primarily composed of connective tissue known as the sclera and cornea

fovea
: exact center of the retina at which visual stimuli are focused for maximal acuity, where the retina is thinnest, at which there is nothing but photoreceptors

free nerve ending
: configuration of a sensory receptor neuron with dendrites in the connective tissue of the organ, such as in the dermis of the skin, that are most often sensitive to chemical, thermal, and mechanical stimuli

general sense
: any sensory system that is distributed throughout the body and incorporated into organs of multiple other systems, such as the walls of the digestive organs or the skin

gustation
: sense of taste

gustatory receptor cells
: sensory cells in the taste bud that transduce the chemical stimuli of gustation

hair cells
: mechanoreceptor cells found in the inner ear that transduce stimuli for the senses of hearing and balance

incus
: (also, anvil) ossicle of the middle ear that connects the malleus to the stapes

inferior oblique
: extraocular muscle responsible for lateral rotation of the eye

inferior rectus
: extraocular muscle responsible for looking down

inner ear
: structure within the temporal bone that contains the sensory apparati of hearing and balance

inner segment
: in the eye, the section of a photoreceptor that contains the nucleus and other major organelles for normal cellular functions

inner synaptic layer
: layer in the retina where bipolar cells connect to RGCs

interoceptor
: sensory receptor that is positioned to interpret stimuli from internal organs, such as stretch receptors in the wall of blood vessels

ipsilateral
: word meaning on the same side, as in axons that do not cross the midline in a fiber tract

iris
: colored portion of the anterior eye that surrounds the pupil

kinesthesia

sense of body movement based on sensations in skeletal muscles, tendons, joints, and the skin

lacrimal duct
: duct in the medial corner of the orbit that drains tears into the nasal cavity

lacrimal gland
: gland lateral to the orbit that produces tears to wash across the surface of the eye

lateral rectus
: extraocular muscle responsible for abduction of the eye

lens
: component of the eye that focuses light on the retina

levator palpebrae superioris
: muscle that causes elevation of the upper eyelid, controlled by fibers in the oculomotor nerve

macula
: enlargement at the base of a semicircular canal at which transduction of equilibrium stimuli takes place within the ampulla

malleus
: (also, hammer) ossicle that is directly

attached to the tympanic membrane

mechanoreceptor
: receptor cell that transduces mechanical stimuli into an electrochemical signal

medial rectus
: extraocular muscle responsible for adduction of the eye

middle ear
: space within the temporal bone between the ear canal and bony labyrinth where the ossicles amplify sound waves from the tympanic membrane to the oval window

neural tunic
: layer of the eye that contains nervous tissue, namely the retina

nociceptor
: receptor cell that senses pain stimuli

odorant molecules
: volatile chemicals that bind to receptor proteins in olfactory neurons to stimulate the sense of smell

olfaction
: sense of smell

olfactory bulb
: central target of the first cranial nerve;

located on the ventral surface of the frontal lobe in the cerebrum

olfactory epithelium
: region of the nasal epithelium where olfactory neurons are located

olfactory sensory neuron
: receptor cell of the olfactory system, sensitive to the chemical stimuli of smell, the axons of which compose the first cranial nerve

opsin
: protein that contains the photosensitive cofactor retinal for phototransduction

optic disc
: spot on the retina at which RGC axons leave the eye and blood vessels of the inner retina pass

optic nerve
: second cranial nerve, which is responsible visual sensation

organ of Corti
: structure in the cochlea in which hair cells transduce movements from sound waves into electrochemical signals

osmoreceptor
: receptor cell that senses differences in the

concentrations of bodily fluids on the basis of osmotic pressure

ossicles
: three small bones in the middle ear

otolith
: layer of calcium carbonate crystals located on top of the otolithic membrane

otolithic membrane
: gelatinous substance in the utricle and saccule of the inner ear that contains calcium carbonate crystals and into which the stereocilia of hair cells are embedded

outer segment
: in the eye, the section of a photoreceptor that contains opsin molecules that transduce light stimuli

outer synaptic layer
: layer in the retina at which photoreceptors connect to bipolar cells

oval window
: membrane at the base of the cochlea where the stapes attaches, marking the beginning of the scala vestibuli

palpebral conjunctiva
: membrane attached to the inner surface of

the eyelids that covers the anterior surface of the cornea

papilla
: for gustation, a bump-like projection on the surface of the tongue that contains taste buds

photoisomerization
: chemical change in the retinal molecule that alters the bonding so that it switches from the 11-*cis*-retinal isomer to the all-*trans*-retinal isomer

photon
: individual “packet” of light

photoreceptor
: receptor cell specialized to respond to light stimuli

proprioception
: sense of position and movement of the body

proprioceptor
: receptor cell that senses changes in the position and kinesthetic aspects of the body

pupil
: open hole at the center of the iris that light passes through into the eye

receptor cell
: cell that transduces environmental stimuli

into neural signals

retina
: nervous tissue of the eye at which phototransduction takes place

retinal
: cofactor in an opsin molecule that undergoes a biochemical change when struck by a photon (pronounced with a stress on the last syllable)

retinal ganglion cell (RGC)
: neuron of the retina that projects along the second cranial nerve

rhodopsin
: photopigment molecule found in the rod photoreceptors

rod photoreceptor
: one of the two types of retinal receptor cell that is specialized for low-light vision

round window
: membrane that marks the end of the scala tympani

saccule
: structure of the inner ear responsible for transducing linear acceleration in the vertical plane

scala tympani
: portion of the cochlea that extends from the apex to the round window

scala vestibuli
: portion of the cochlea that extends from the oval window to the apex

sclera
: white of the eye

semicircular canals
: structures within the inner ear responsible for transducing rotational movement information

sensory modality
: a particular system for interpreting and perceiving environmental stimuli by the nervous system

somatosensation
: general sense associated with modalities lumped together as touch

special sense
: any sensory system associated with a specific organ structure, namely smell, taste, sight, hearing, and balance

spiral ganglion
: location of neuronal cell bodies that transmit auditory information along the eighth cranial

nerve

stapes
: (also, stirrup) ossicle of the middle ear that is attached to the inner ear

stereocilia
: array of apical membrane extensions in a hair cell that transduce movements when they are bent

submodality
: specific sense within a broader major sense such as sweet as a part of the sense of taste, or color as a part of vision

superior oblique
: extraocular muscle responsible for medial rotation of the eye

superior rectus
: extraocular muscle responsible for looking up

taste buds
: structures within a papilla on the tongue that contain gustatory receptor cells

tectorial membrane
: component of the organ of Corti that lays over the hair cells, into which the stereocilia are embedded

thermoreceptor

sensory receptor specialized for temperature stimuli

topographical
: relating to positional information

transduction
: process of changing an environmental stimulus into the electrochemical signals of the nervous system

trochlea
: cartilaginous structure that acts like a pulley for the superior oblique muscle

tympanic membrane
: ear drum

umami
: taste submodality for sensitivity to the concentration of amino acids; also called the savory sense

utricle
: structure of the inner ear responsible for transducing linear acceleration in the horizontal plane

vascular tunic
: middle layer of the eye primarily composed of connective tissue with a rich blood supply

vestibular ganglion

location of neuronal cell bodies that transmit equilibrium information along the eighth cranial nerve

vestibule
: in the ear, the portion of the inner ear responsible for the sense of equilibrium

visceral sense
: sense associated with the internal organs

vision
: special sense of sight based on transduction of light stimuli

visual acuity
: property of vision related to the sharpness of focus, which varies in relation to retinal position

vitreous humor
: viscous fluid that fills the posterior chamber of the eye

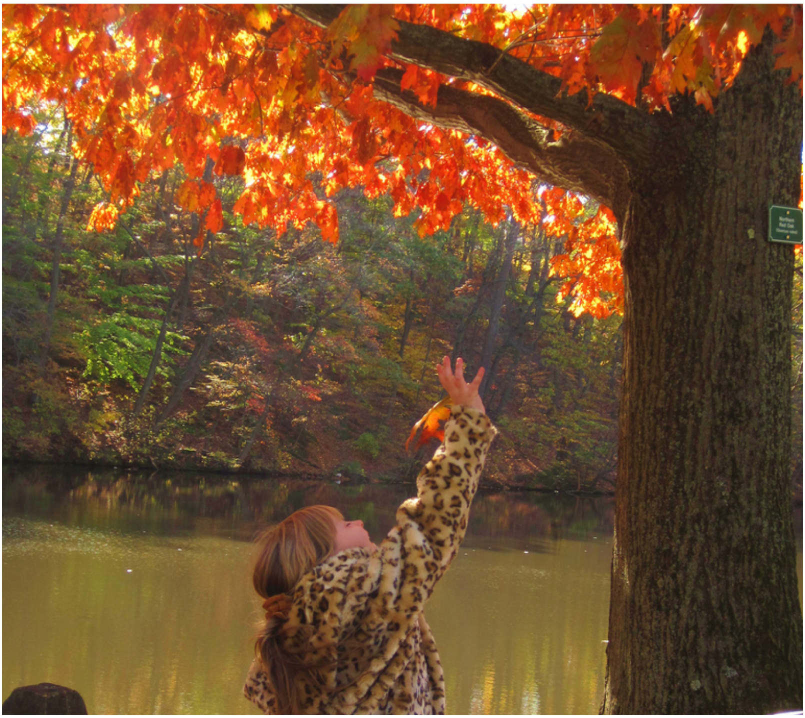
zonule fibers
: fibrous connections between the ciliary body and the lens

Introduction

class="introduction"

A Child Catches a Falling Leaf

Hormones of the endocrine system coordinate and control growth, metabolism, temperature regulation, the stress response, reproduction, and many other functions. (credit: “seenthroughmylense”/flickr.com)



Chapter Objectives

After studying this chapter, you will be able to:

- Identify the contributions of the endocrine

system to homeostasis
- Discuss the chemical composition of hormones and the mechanisms of hormone action
- Summarize the site of production, regulation, and effects of the hormones of the pituitary, thyroid, parathyroid, adrenal, and pineal glands
- Discuss the hormonal regulation of the reproductive system
- Explain the role of the pancreatic endocrine cells in the regulation of blood glucose
- Identify the hormones released by the heart, kidneys, and other organs with secondary endocrine functions
- Discuss several common diseases associated with endocrine system dysfunction
- Discuss the embryonic development of, and the effects of aging on, the endocrine system

You may never have thought of it this way, but when you send a text message to two friends to meet you at the dining hall at six, you're sending digital signals that (you hope) will affect their behavior—even though they are some distance away. Similarly, certain cells send chemical signals to other cells in the body that influence their behavior. This long-distance intercellular communication, coordination, and control is critical for homeostasis, and it is the fundamental function

of the endocrine system.

An Overview of the Endocrine System

By the end of this section, you will be able to:

- Distinguish the types of intercellular communication, their importance, mechanisms, and effects
- Identify the major organs and tissues of the endocrine system and their location in the body

Communication is a process in which a sender transmits signals to one or more receivers to control and coordinate actions. In the human body, two major organ systems participate in relatively "long distance" communication: the nervous system and the endocrine system. Together, these two systems are primarily responsible for maintaining homeostasis in the body.

Neural and Endocrine Signaling

The nervous system uses two types of intercellular communication—electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters such as serotonin or norepinephrine. Neurotransmitters act locally and rapidly. When an electrical signal in the form of an action potential arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap

between a sending neuron and a receiving neuron or muscle cell). Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response. The target cell responds within milliseconds of receiving the chemical “message”; this response then ceases very quickly once the neural signaling ends. In this way, neural communication enables body functions that involve quick, brief actions, such as movement, sensation, and cognition.In contrast, the **endocrine system** uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the **hormone**—into the extracellular fluid. Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response. As a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones. For example, the hormones released when you are confronted with a dangerous or frightening situation, called the fight-or-flight response, occur by the release of adrenal hormones—epinephrine and norepinephrine—within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

Visit this link to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?

In addition, endocrine signaling is typically less specific than neural signaling. The same hormone may play a role in a variety of different physiological processes depending on the target cells involved. For example, the hormone oxytocin promotes uterine contractions in women in labor. It is also important in breastfeeding, and may be involved in the sexual response and in feelings of emotional attachment in both males and females.

In general, the nervous system involves quick responses to rapid changes in the external environment, and the endocrine system is usually slower acting—taking care of the internal environment of the body, maintaining homeostasis,

and controlling reproduction ([link]). So how does the fight-or-flight response that was mentioned earlier happen so quickly if hormones are usually slower acting? It is because the two systems are connected. It is the fast action of the nervous system in response to the danger in the environment that stimulates the adrenal glands to secrete their hormones. As a result, the nervous system can cause rapid endocrine responses to keep up with sudden changes in both the external and internal environments when necessary.

Endocrine and Nervous Systems

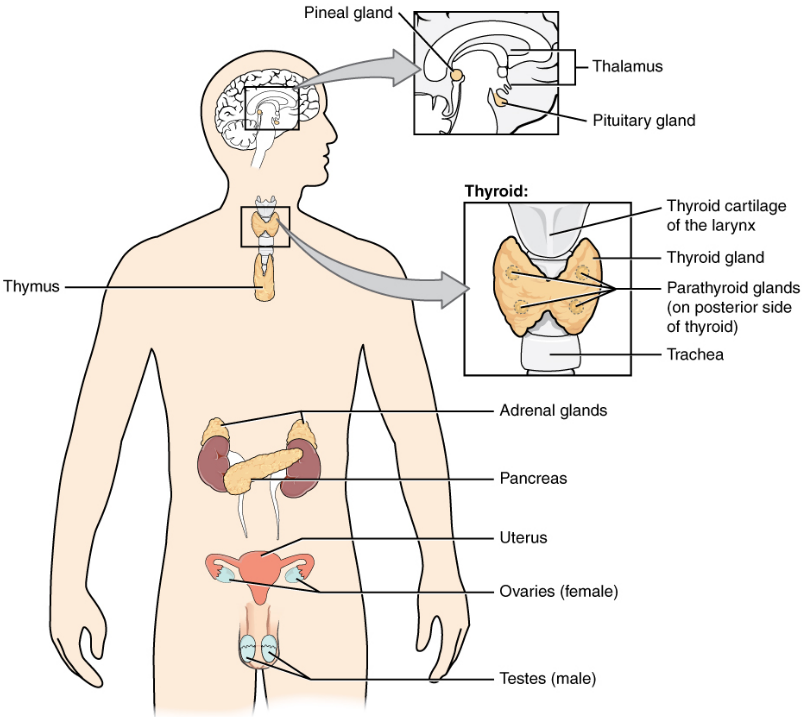
	Endocrine system	**Nervous system**
Signaling mechanism(s)	Chemical	Chemical/ electrical
Primary chemical signal	Hormones	Neurotransmitters
Distance traveled	Long or short	Always short
Response time	Fast or slow	Always fast
Environment targeted	Internal	Internal and external

Structures of the Endocrine System

The endocrine system consists of cells, tissues, and organs that secrete hormones as a primary or secondary function. The **endocrine gland** is the major player in this system. The primary function of these ductless glands is to secrete their hormones directly into the surrounding fluid. The interstitial fluid and the blood vessels then transport the hormones throughout the body. The endocrine system includes the pituitary, thyroid, parathyroid, adrenal, and pineal glands ([link]). Some of these glands have both endocrine and non-endocrine functions. For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels. The hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, female ovaries, and male testes are other organs that contain cells with endocrine function. Moreover, adipose tissue has long been known to produce hormones, and recent research has revealed that even bone tissue has endocrine functions.

Endocrine System

Endocrine glands and cells are located throughout the body and play an important role in homeostasis.



The ductless endocrine glands are not to be confused with the body's **exocrine system**, whose glands release their secretions through ducts. Examples of exocrine glands include the sebaceous and sweat glands of the skin. As just noted, the pancreas also has an exocrine function: most of its cells secrete pancreatic juice through the pancreatic and accessory ducts to the lumen of the small intestine.

Other Types of Chemical Signaling

In endocrine signaling, hormones secreted into the

extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body. In contrast, autocrine signaling takes place within the same cell. An **autocrine** (auto- = "self") is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the province of the **paracrine**, also called a paracrine factor, which is a chemical that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways. Another example is the neurotransmitters of the nervous system, which act only locally within the synaptic cleft.

Career Connections

Endocrinologist

Endocrinology is a specialty in the field of medicine that focuses on the treatment of

endocrine system disorders. Endocrinologists—medical doctors who specialize in this field—are experts in treating diseases associated with hormonal systems, ranging from thyroid disease to diabetes mellitus. Endocrine surgeons treat endocrine disease through the removal, or resection, of the affected endocrine gland.

Patients who are referred to endocrinologists may have signs and symptoms or blood test results that suggest excessive or impaired functioning of an endocrine gland or endocrine cells. The endocrinologist may order additional blood tests to determine whether the patient's hormonal levels are abnormal, or they may stimulate or suppress the function of the suspect endocrine gland and then have blood taken for analysis. Treatment varies according to the diagnosis. Some endocrine disorders, such as type 2 diabetes, may respond to lifestyle changes such as modest weight loss, adoption of a healthy diet, and regular physical activity. Other disorders may require medication, such as hormone replacement, and routine monitoring by the endocrinologist. These include disorders of the pituitary gland that can affect growth and disorders of the thyroid gland that can result in a variety of metabolic problems.

Some patients experience health problems as a result of the normal decline in hormones that can accompany aging. These patients can consult with an endocrinologist to weigh the risks and benefits of hormone replacement therapy intended to boost

their natural levels of reproductive hormones. In addition to treating patients, endocrinologists may be involved in research to improve the understanding of endocrine system disorders and develop new treatments for these diseases.

Chapter Review

The endocrine system consists of cells, tissues, and organs that secrete hormones critical to homeostasis. The body coordinates its functions through two major types of communication: neural and endocrine. Neural communication includes both electrical and chemical signaling between neurons and target cells. Endocrine communication involves chemical signaling via the release of hormones into the extracellular fluid. From there, hormones diffuse into the bloodstream and may travel to distant body regions, where they elicit a response in target cells. Endocrine glands are ductless glands that secrete hormones. Many organs of the body with other primary functions—such as the heart, stomach, and kidneys—also have hormone-secreting cells.

Interactive Link Questions

Visit this link to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?

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cAMP

Review Questions

Endocrine glands _____.

1. secrete hormones that travel through a duct to the target organs
2. release neurotransmitters into the synaptic cleft
3. secrete chemical messengers that travel in the bloodstream
4. include sebaceous glands and sweat glands

C

Chemical signaling that affects neighboring cells is called _____.

1. autocrine
2. paracrine
3. endocrine
4. neuron

B

Critical Thinking Questions

Describe several main differences in the communication methods used by the endocrine system and the nervous system.

The endocrine system uses chemical signals called hormones to convey information from one part of the body to a distant part of the body. Hormones are released from the endocrine cell into the extracellular environment, but then travel in the bloodstream to target tissues. This communication and response can take seconds to days. In contrast, neurons transmit electrical signals along their axons. At the axon terminal, the electrical signal prompts the release of a chemical signal called a neurotransmitter that carries the message across the synaptic cleft to elicit a

response in the neighboring cell. This method of communication is nearly instantaneous, of very brief duration, and is highly specific.

Compare and contrast endocrine and exocrine glands.

Endocrine glands are ductless. They release their secretion into the surrounding fluid, from which it enters the bloodstream or lymph to travel to distant cells. Moreover, the secretions of endocrine glands are hormones. Exocrine glands release their secretions through a duct that delivers the secretion to the target location. Moreover, the secretions of exocrine glands are not hormones, but compounds that have an immediate physiologic function. For example, pancreatic juice contains enzymes that help digest food.

True or false: Neurotransmitters are a special class of paracrines. Explain your answer.

True. Neurotransmitters can be classified as paracrines because, upon their release from a neuron’s axon terminals, they travel across a microscopically small cleft to exert their effect on a nearby neuron or muscle cell.

Glossary

autocrine
: chemical signal that elicits a response in the same cell that secreted it

endocrine gland
: tissue or organ that secretes hormones into the blood and lymph without ducts such that they may be transported to organs distant from the site of secretion

endocrine system
: cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes

exocrine system
: cells, tissues, and organs that secrete substances directly to target tissues via glandular ducts

hormone
: secretion of an endocrine organ that travels via the bloodstream or lymphatics to induce a response in target cells or tissues in another part of the body

paracrine
: chemical signal that elicits a response in neighboring cells; also called paracrine factor

Hormones

By the end of this section, you will be able to:

- Identify the three major classes of hormones on the basis of chemical structure
- Compare and contrast intracellular and cell membrane hormone receptors
- Describe signaling pathways that involve cAMP and IP3
- Identify several factors that influence a target cell's response
- Discuss the role of feedback loops and humoral, hormonal, and neural stimuli in hormone control

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell's response. Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many other body functions. The major hormones of the human body and their effects are identified in [link].

Endocrine Glands and Their Major Hormones

Endocrine gland	**Associated hormones**	**Chemical class**	**Effect**
Pituitary (anterior)	Growth hormone (GH)	Protein	Promotes growth of body tissues
Pituitary (anterior)	Prolactin (PRL)	Peptide	Promotes milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone	Peptide	Stimulates water

	(ADH)		reabsorption by kidneys
Pituitary (posterior)	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Thyroid	Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduces blood Ca^{2+} levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca^{2+} levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na^{+} levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles
Pancreas	Insulin	Protein	Reduces

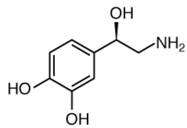
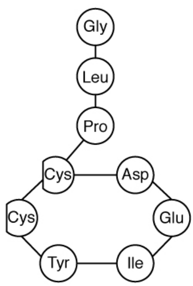
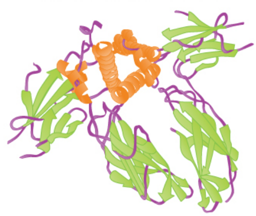
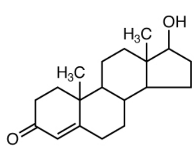
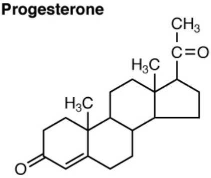
			blood glucose levels
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of male secondary sex characteristics and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of female secondary sex characteristics and prepare the body for childbirth

Types of Hormones

The hormones of the human body can be divided into two major groups on the basis of their chemical

structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids ([link]). These chemical groups affect a hormone’s distribution, the type of receptors it binds to, and other aspects of its function.

Amine, Peptide, Protein, and Steroid Hormone Structure

Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine’s carboxyl group is replaced with a benzene ring)	**Norepinephrine** 
Peptide Hormone	Short chains of linked amino acids	**Oxytocin** 
Protein Hormone	Long chains of linked amino acids	**Human Growth Hormone** 
Steroid Hormones	Derived from the lipid cholesterol	**Testosterone**  **Progesterone** 

Amine Hormones

Hormones derived from the modification of amino acids are referred to as amine hormones. Typically, the original structure of the amino acid is modified such that a –COOH, or carboxyl, group is removed, whereas the $-NH_3^+$, or amine, group remains.

Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm. Tyrosine derivatives include the metabolism-regulating thyroid hormones, as well as the catecholamines, such as epinephrine, norepinephrine, and dopamine. Epinephrine and norepinephrine are secreted by the adrenal medulla and play a role in the fight-or-flight response, whereas dopamine is secreted by the hypothalamus and inhibits the release of certain anterior pituitary hormones.

Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into

mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

Steroid Hormones

The primary hormones derived from lipids are steroids. Steroid hormones are derived from the lipid cholesterol. For example, the reproductive hormones testosterone and the estrogens—which are produced by the gonads (testes and ovaries)—are steroid hormones. The adrenal glands produce the steroid hormone aldosterone, which is involved in osmoregulation, and cortisol, which plays a role in metabolism.

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel to their target cell bound to a transport protein. This

more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. A hormone’s half-life is the time required for half the concentration of the hormone to be degraded. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid–derived hormone epinephrine has a half-life of approximately one minute.

Pathways of Hormone Action

The message a hormone sends is received by a **hormone receptor**, a protein located either inside the cell or within the cell membrane. The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell’s response. Hormone receptors recognize molecules with specific shapes and side groups, and respond only to those hormones that are recognized. The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses. Thus, the response triggered by a hormone depends not only on the hormone, but also on the target cell.

Once the target cell receives the hormone signal, it can respond in a variety of ways. The response may include the stimulation of protein synthesis,

activation or deactivation of enzymes, alteration in the permeability of the cell membrane, altered rates of mitosis and cell growth, and stimulation of the secretion of products. Moreover, a single hormone may be capable of inducing different responses in a given cell.

Pathways Involving Intracellular Hormone Receptors

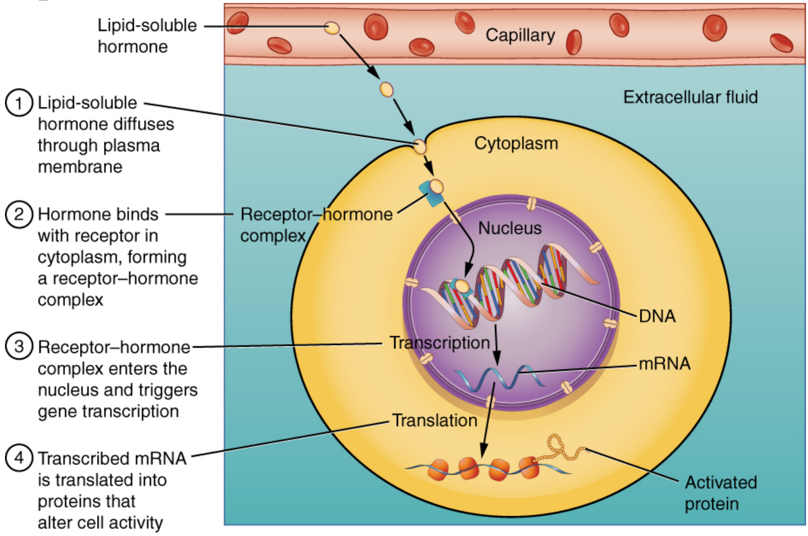
Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor ([link]). Thyroid hormones, which contain benzene rings studded with iodine, are also lipid-soluble and can enter the cell.

The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to a particular segment of the cell's DNA. In contrast, thyroid hormones bind to receptors already bound to DNA. For both steroid and thyroid hormones, binding of the hormone-receptor complex with DNA triggers transcription of a target gene to mRNA, which

moves to the cytosol and directs protein synthesis by ribosomes.

Binding of Lipid-Soluble Hormones

A steroid hormone directly initiates the production of proteins within a target cell. Steroid hormones easily diffuse through the cell membrane. The hormone binds to its receptor in the cytosol, forming a receptor–hormone complex. The receptor–hormone complex then enters the nucleus and binds to the target gene on the DNA. Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm.



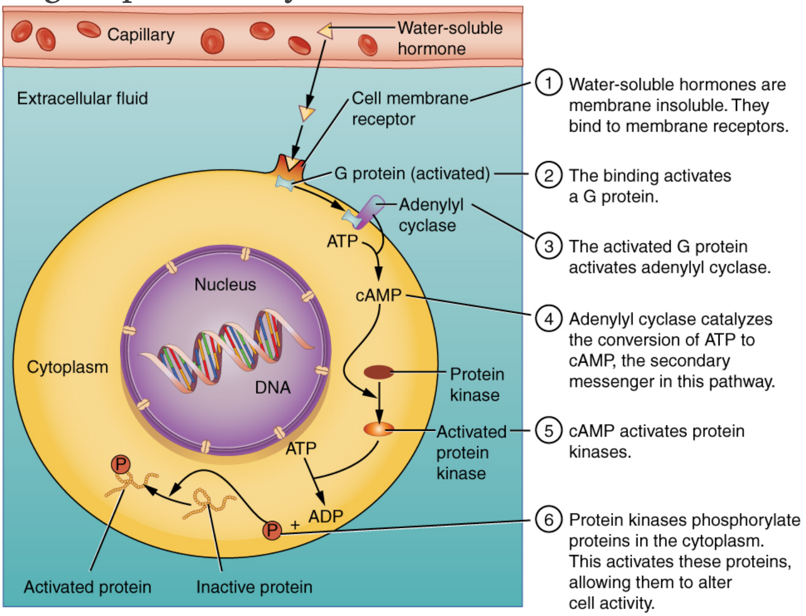
Pathways Involving Cell Membrane Hormone Receptors

Hydrophilic, or water-soluble, hormones are unable to diffuse through the lipid bilayer of the cell

membrane and must therefore pass on their message to a receptor located at the surface of the cell. Except for thyroid hormones, which are lipid-soluble, all amino acid–derived hormones bind to cell membrane receptors that are located, at least in part, on the extracellular surface of the cell membrane. Therefore, they do not directly affect the transcription of target genes, but instead initiate a signaling cascade that is carried out by a molecule called a **second messenger**. In this case, the hormone is called a **first messenger**.

The second messenger used by most hormones is **cyclic adenosine monophosphate (cAMP)**. In the cAMP second messenger system, a water-soluble hormone binds to its receptor in the cell membrane (Step 1 in [link]). This receptor is associated with an intracellular component called a **G protein**, and binding of the hormone activates the G-protein component (Step 2). The activated G protein in turn activates an enzyme called **adenylyl cyclase**, also known as adenylate cyclase (Step 3), which converts adenosine triphosphate (ATP) to cAMP (Step 4). As the second messenger, cAMP activates a type of enzyme called a **protein kinase** that is present in the cytosol (Step 5). Activated protein kinases initiate a **phosphorylation cascade**, in which multiple protein kinases phosphorylate (add a phosphate group to) numerous and various cellular proteins, including other enzymes (Step 6).
Binding of Water-Soluble Hormones

Water-soluble hormones cannot diffuse through the cell membrane. These hormones must bind to a surface cell-membrane receptor. The receptor then initiates a cell-signaling pathway within the cell involving G proteins, adenylyl cyclase, the secondary messenger cyclic AMP (cAMP), and protein kinases. In the final step, these protein kinases phosphorylate proteins in the cytoplasm. This activates proteins in the cell that carry out the changes specified by the hormone.



The phosphorylation of cellular proteins can trigger a wide variety of effects, from nutrient metabolism to the synthesis of different hormones and other products. The effects vary according to the type of target cell, the G proteins and kinases involved, and the phosphorylation of proteins. Examples of hormones that use cAMP as a second messenger

include calcitonin, which is important for bone construction and regulating blood calcium levels; glucagon, which plays a role in blood glucose levels; and thyroid-stimulating hormone, which causes the release of T_3 and T_4 from the thyroid gland.

Overall, the phosphorylation cascade significantly increases the efficiency, speed, and specificity of the hormonal response, as thousands of signaling events can be initiated simultaneously in response to a very low concentration of hormone in the bloodstream. However, the duration of the hormone signal is short, as cAMP is quickly deactivated by the enzyme **phosphodiesterase (PDE)**, which is located in the cytosol. The action of PDE helps to ensure that a target cell's response ceases quickly unless new hormones arrive at the cell membrane.

Importantly, there are also G proteins that decrease the levels of cAMP in the cell in response to hormone binding. For example, when growth hormone–inhibiting hormone (GHIH), also known as somatostatin, binds to its receptors in the pituitary gland, the level of cAMP decreases, thereby inhibiting the secretion of human growth hormone.

Not all water-soluble hormones initiate the cAMP second messenger system. One common alternative system uses calcium ions as a second messenger. In this system, G proteins activate the enzyme phospholipase C (PLC), which functions similarly to

adenylyl cyclase. Once activated, PLC cleaves a membrane-bound phospholipid into two molecules: **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)**. Like cAMP, DAG activates protein kinases that initiate a phosphorylation cascade. At the same time, IP_3 causes calcium ions to be released from storage sites within the cytosol, such as from within the smooth endoplasmic reticulum. The calcium ions then act as second messengers in two ways: they can influence enzymatic and other cellular activities directly, or they can bind to calcium-binding proteins, the most common of which is calmodulin. Upon binding calcium, calmodulin is able to modulate protein kinase within the cell. Examples of hormones that use calcium ions as a second messenger system include angiotensin II, which helps regulate blood pressure through vasoconstriction, and growth hormone–releasing hormone (GHRH), which causes the pituitary gland to release growth hormones.

Factors Affecting Target Cell Response

You will recall that target cells must have receptors specific to a given hormone if that hormone is to trigger a response. But several other factors influence the target cell response. For example, the presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that

hormone. This process is called **downregulation**, and it allows cells to become less reactive to the excessive hormone levels. When the level of a hormone is chronically reduced, target cells engage in **upregulation** to increase their number of receptors. This process allows cells to be more sensitive to the hormone that is present. Cells can also alter the sensitivity of the receptors themselves to various hormones.

Two or more hormones can interact to affect the response of cells in a variety of ways. The three most common types of interaction are as follows:

- The permissive effect, in which the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. A dietary deficiency of iodine, a component of thyroid hormones, can therefore affect reproductive system development and functioning.
- The synergistic effect, in which two hormones with similar effects produce an amplified response. In some cases, two hormones are required for an adequate response. For example, two different reproductive hormones —FSH from the pituitary gland and estrogens from the ovaries—are required for the maturation of female ova (egg cells).
- The antagonistic effect, in which two hormones

have opposing effects. A familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

Regulation of Hormone Secretion

To prevent abnormal hormone levels and a potential disease state, hormone levels must be tightly controlled. The body maintains this control by balancing hormone production and degradation. Feedback loops govern the initiation and maintenance of most hormone secretion in response to various stimuli.

Role of Feedback Loops

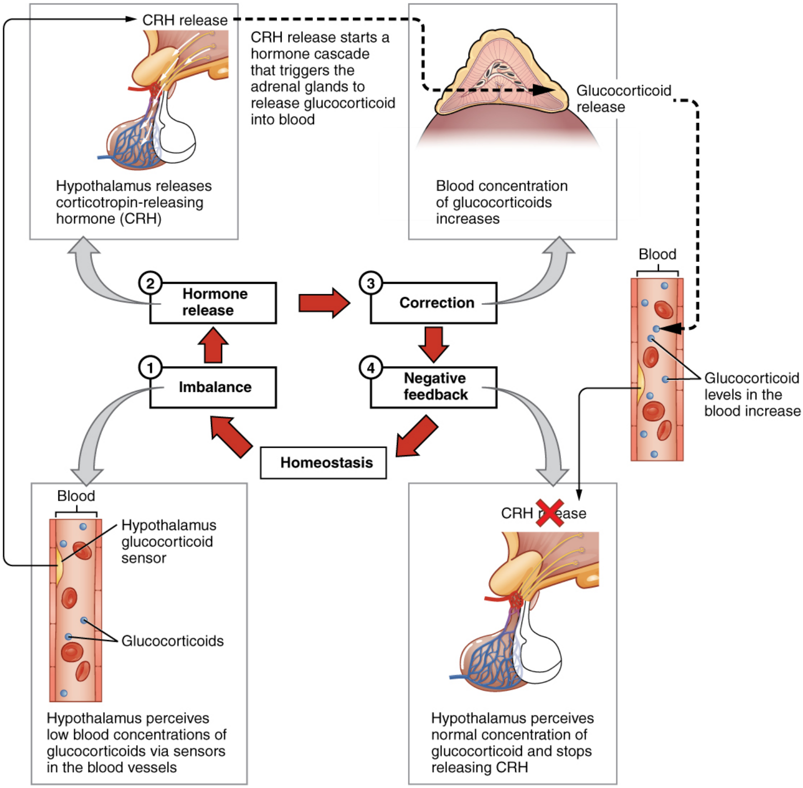
The contribution of feedback loops to homeostasis will only be briefly reviewed here. Positive feedback loops are characterized by the release of additional hormone in response to an original hormone release. The release of oxytocin during childbirth is a positive feedback loop. The initial release of oxytocin begins to signal the uterine muscles to contract, which pushes the fetus toward the cervix, causing it to stretch. This, in turn, signals the

pituitary gland to release more oxytocin, causing labor contractions to intensify. The release of oxytocin decreases after the birth of the child.

The more common method of hormone regulation is the negative feedback loop. Negative feedback is characterized by the inhibition of further secretion of a hormone in response to adequate levels of that hormone. This allows blood levels of the hormone to be regulated within a narrow range. An example of a negative feedback loop is the release of glucocorticoid hormones from the adrenal glands, as directed by the hypothalamus and pituitary gland. As glucocorticoid concentrations in the blood rise, the hypothalamus and pituitary gland reduce their signaling to the adrenal glands to prevent additional glucocorticoid secretion ([link]).

Negative Feedback Loop

The release of adrenal glucocorticoids is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.



Role of Endocrine Gland Stimuli

Reflexes triggered by both chemical and neural stimuli control endocrine activity. These reflexes may be simple, involving only one hormone response, or they may be more complex and involve many hormones, as is the case with the hypothalamic control of various anterior pituitary–controlled hormones.

Humoral stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions, which

cause the release or inhibition of a hormone to, in turn, maintain homeostasis. For example, osmoreceptors in the hypothalamus detect changes in blood osmolarity (the concentration of solutes in the blood plasma). If blood osmolarity is too high, meaning that the blood is not dilute enough, osmoreceptors signal the hypothalamus to release ADH. The hormone causes the kidneys to reabsorb more water and reduce the volume of urine produced. This reabsorption causes a reduction of the osmolarity of the blood, diluting the blood to the appropriate level. The regulation of blood glucose is another example. High blood glucose levels cause the release of insulin from the pancreas, which increases glucose uptake by cells and liver storage of glucose as glycogen.

An endocrine gland may also secrete a hormone in response to the presence of another hormone produced by a different endocrine gland. Such hormonal stimuli often involve the hypothalamus, which produces releasing and inhibiting hormones that control the secretion of a variety of pituitary hormones.

In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal

glands to secrete norepinephrine and epinephrine. The two hormones dilate blood vessels, increase the heart and respiratory rate, and suppress the digestive and immune systems. These responses boost the body’s transport of oxygen to the brain and muscles, thereby improving the body’s ability to fight or flee.

Everyday Connections

Bisphenol A and Endocrine Disruption

You may have heard news reports about the effects of a chemical called bisphenol A (BPA) in various types of food packaging. BPA is used in the manufacturing of hard plastics and epoxy resins. Common food-related items that may contain BPA include the lining of aluminum cans, plastic food-storage containers, drinking cups, as well as baby bottles and “sippy” cups. Other uses of BPA include medical equipment, dental fillings, and the lining of water pipes.

Research suggests that BPA is an endocrine disruptor, meaning that it negatively interferes with the endocrine system, particularly during the prenatal and postnatal development period. In particular, BPA mimics the hormonal effects of estrogens and has the opposite effect—that of androgens. The U.S. Food and Drug Administration (FDA) notes in their statement about BPA safety that although traditional toxicology studies have

supported the safety of low levels of exposure to BPA, recent studies using novel approaches to test for subtle effects have led to some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. The FDA is currently facilitating decreased use of BPA in food-related materials. Many US companies have voluntarily removed BPA from baby bottles, "sippy" cups, and the linings of infant formula cans, and most plastic reusable water bottles sold today boast that they are "BPA free." In contrast, both Canada and the European Union have completely banned the use of BPA in baby products.

The potential harmful effects of BPA have been studied in both animal models and humans and include a large variety of health effects, such as developmental delay and disease. For example, prenatal exposure to BPA during the first trimester of human pregnancy may be associated with wheezing and aggressive behavior during childhood. Adults exposed to high levels of BPA may experience altered thyroid signaling and male sexual dysfunction. BPA exposure during the prenatal or postnatal period of development in animal models has been observed to cause neurological delays, changes in brain structure and function, sexual dysfunction, asthma, and increased risk for multiple cancers. In vitro studies have also shown that BPA exposure causes molecular changes that initiate the development of cancers of the

breast, prostate, and brain. Although these studies have implicated BPA in numerous ill health effects, some experts caution that some of these studies may be flawed and that more research needs to be done. In the meantime, the FDA recommends that consumers take precautions to limit their exposure to BPA. In addition to purchasing foods in packaging free of BPA, consumers should avoid carrying or storing foods or liquids in bottles with the recycling code 3 or 7. Foods and liquids should not be microwave-heated in any form of plastic: use paper, glass, or ceramics instead.

Chapter Review

Hormones are derived from amino acids or lipids. Amine hormones originate from the amino acids tryptophan or tyrosine. Larger amino acid hormones include peptides and protein hormones. Steroid hormones are derived from cholesterol.

Steroid hormones and thyroid hormone are lipid soluble. All other amino acid–derived hormones are water soluble. Hydrophobic hormones are able to diffuse through the membrane and interact with an intracellular receptor. In contrast, hydrophilic hormones must interact with cell membrane

receptors. These are typically associated with a G protein, which becomes activated when the hormone binds the receptor. This initiates a signaling cascade that involves a second messenger, such as cyclic adenosine monophosphate (cAMP). Second messenger systems greatly amplify the hormone signal, creating a broader, more efficient, and faster response.

Hormones are released upon stimulation that is of either chemical or neural origin. Regulation of hormone release is primarily achieved through negative feedback. Various stimuli may cause the release of hormones, but there are three major types. Humoral stimuli are changes in ion or nutrient levels in the blood. Hormonal stimuli are changes in hormone levels that initiate or inhibit the secretion of another hormone. Finally, a neural stimulus occurs when a nerve impulse prompts the secretion or inhibition of a hormone.

Review Questions

A newly developed pesticide has been observed to bind to an intracellular hormone receptor. If ingested, residue from this pesticide could disrupt levels of ______.

1. melatonin
2. thyroid hormone
3. growth hormone
4. insulin

B

A small molecule binds to a G protein, preventing its activation. What direct effect will this have on signaling that involves cAMP?

1. The hormone will not be able to bind to the hormone receptor.
2. Adenylyl cyclase will not be activated.
3. Excessive quantities of cAMP will be produced.
4. The phosphorylation cascade will be initiated.

B

A student is in a car accident, and although not hurt, immediately experiences pupil dilation, increased heart rate, and rapid breathing. What type of endocrine system stimulus did the student receive?

1. humoral

2. hormonal
3. neural
4. positive feedback

C

Critical Thinking Questions

Compare and contrast the signaling events involved with the second messengers cAMP and IP_3.

In both cAMP and IP_3–calcium signaling, a hormone binds to a cell membrane hormone receptor that is coupled to a G protein. The G protein becomes activated when the hormone binds. In the case of cAMP signaling, the activated G protein activates adenylyl cyclase, which causes ATP to be converted to cAMP. This second messenger can then initiate other signaling events, such as a phosphorylation cascade. In the case of IP_3–calcium signaling, the activated G protein activates phospholipase C, which cleaves a membrane phospholipid compound into DAG and IP_3. IP_3 causes the release of calcium, another second messenger,

from intracellular stores. This causes further signaling events.

Describe the mechanism of hormone response resulting from the binding of a hormone with an intracellular receptor.

An intracellular hormone receptor is located within the cell. A hydrophobic hormone diffuses through the cell membrane and binds to the intracellular hormone receptor, which may be in the cytosol or in the cell nucleus. This hormone–receptor complex binds to a segment of DNA. This initiates the transcription of a target gene, the end result of which is protein assembly and the hormonal response.

Glossary

adenylyl cyclase
: membrane-bound enzyme that converts ATP to cyclic AMP, creating cAMP, as a result of G-protein activation

cyclic adenosine monophosphate (cAMP)
: second messenger that, in response to adenylyl cyclase activation, triggers a phosphorylation cascade

diacylglycerol (DAG)
: molecule that, like cAMP, activates protein kinases, thereby initiating a phosphorylation cascade

downregulation
: decrease in the number of hormone receptors, typically in response to chronically excessive levels of a hormone

first messenger
: hormone that binds to a cell membrane hormone receptor and triggers activation of a second messenger system

G protein
: protein associated with a cell membrane hormone receptor that initiates the next step in a second messenger system upon activation by hormone–receptor binding

hormone receptor
: protein within a cell or on the cell membrane that binds a hormone, initiating the target cell response

inositol triphosphate (IP_3)
: molecule that initiates the release of calcium ions from intracellular stores

phosphodiesterase (PDE)
: cytosolic enzyme that deactivates and

degrades cAMP

phosphorylation cascade
signaling event in which multiple protein kinases phosphorylate the next protein substrate by transferring a phosphate group from ATP to the protein

protein kinase
enzyme that initiates a phosphorylation cascade upon activation

second messenger
molecule that initiates a signaling cascade in response to hormone binding on a cell membrane receptor and activation of a G protein

upregulation
increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

The Endocrine Pancreas

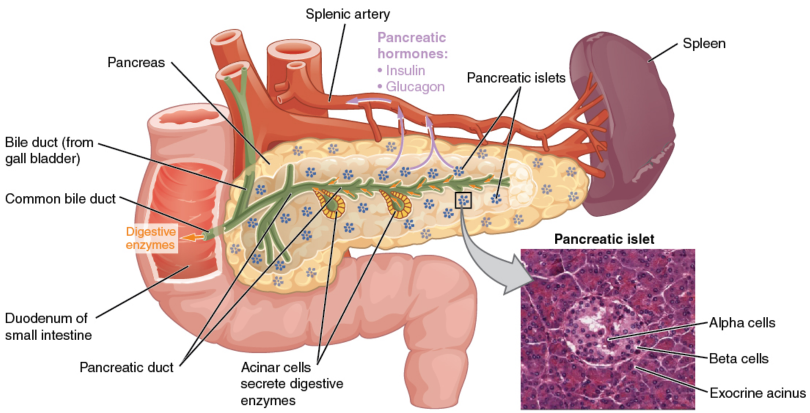
By the end of this section, you will be able to:

- Describe the location and structure of the pancreas, and the morphology and function of the pancreatic islets
- Compare and contrast the functions of insulin and glucagon

The **pancreas** is a long, slender organ, most of which is located posterior to the bottom half of the stomach ([link]). Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its **pancreatic islets**—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

Pancreas

The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail.

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of

cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Receptors located in the pancreas sense blood glucose levels, and subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels.

Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting or during prolonged labor or exercise ([link]). In response, the alpha cells of the pancreas secrete the hormone **glucagon**, which has several effects:

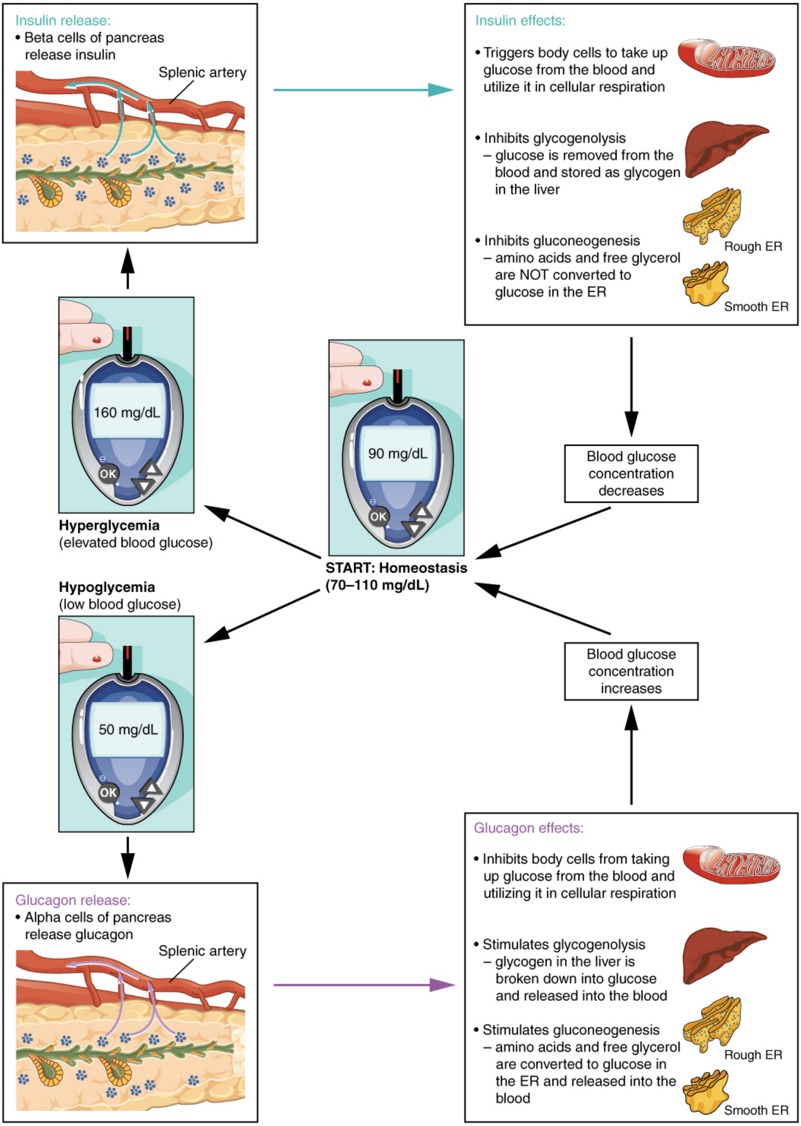
- It stimulates the liver to convert its stores of glycogen back into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids

from the blood and convert them into glucose. This response is known as gluconeogenesis.
- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.

Homeostatic Regulation of Blood Glucose Levels

Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration rises above this range, insulin is released, which stimulates body cells to remove glucose from the blood. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.



Insulin

The primary function of **insulin** is to facilitate the uptake of glucose into body cells. Red blood cells, as well as cells of the brain, liver, kidneys, and the

lining of the small intestine, do not have insulin receptors on their cell membranes and do not require insulin for glucose uptake. Although all other body cells do require insulin if they are to take glucose from the bloodstream, skeletal muscle cells and adipose cells are the primary targets of insulin.

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for insulin production and secretion by the beta cells of the pancreas. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence of insulin, these transport proteins are normally recycled slowly between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move

glucose by facilitated diffusion into the cell interior.

Visit this link to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis. The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, further insulin release is inhibited. The pancreatic hormones are summarized in [link].

Hormones of the Pancreas		
Associated hormones	Chemical class	Effect
Insulin (beta cells)	Protein	Reduces blood glucose levels
Glucagon (alpha cells)	Protein	Increases blood glucose levels
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release
Pancreatic polypeptide (PP cells)	Protein	Role in appetite

Disorders of the…

Endocrine System: Diabetes Mellitus

Dysfunction of insulin production and secretion, as well as the target cells' responsiveness to insulin, can lead to a condition called **diabetes mellitus**. An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be

classified as diabetes.
There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.
Type 2 diabetes accounts for approximately 95 percent of all cases. It is acquired, and lifestyle factors such as poor diet, inactivity, and the presence of pre-diabetes greatly increase a person’s risk. About 80 to 90 percent of people with type 2 diabetes are overweight or obese. In type 2 diabetes, cells become resistant to the effects of insulin. In response, the pancreas increases its insulin secretion, but over time, the beta cells become exhausted. In many cases, type 2 diabetes can be reversed by moderate weight loss, regular physical activity, and consumption of a healthy diet; however, if blood glucose levels cannot be controlled, the diabetic will eventually require insulin.
Two of the early manifestations of diabetes are excessive urination and excessive thirst. They demonstrate how the out-of-control levels of glucose in the blood affect kidney function. The kidneys are responsible for filtering glucose from the blood. Excessive blood glucose draws water

into the urine, and as a result the person eliminates an abnormally large quantity of sweet urine. The use of body water to dilute the urine leaves the body dehydrated, and so the person is unusually and continually thirsty. The person may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream.

Over time, persistently high levels of glucose in the blood injure tissues throughout the body, especially those of the blood vessels and nerves. Inflammation and injury of the lining of arteries lead to atherosclerosis and an increased risk of heart attack and stroke. Damage to the microscopic blood vessels of the kidney impairs kidney function and can lead to kidney failure. Damage to blood vessels that serve the eyes can lead to blindness. Blood vessel damage also reduces circulation to the limbs, whereas nerve damage leads to a loss of sensation, called neuropathy, particularly in the hands and feet. Together, these changes increase the risk of injury, infection, and tissue death (necrosis), contributing to a high rate of toe, foot, and lower leg amputations in people with diabetes. Uncontrolled diabetes can also lead to a dangerous form of metabolic acidosis called ketoacidosis. Deprived of glucose, cells increasingly rely on fat stores for fuel. However, in a glucose-deficient state, the liver is forced to use an alternative lipid metabolism pathway that results in the increased production of ketone bodies (or ketones), which

are acidic. The build-up of ketones in the blood causes ketoacidosis, which—if left untreated—may lead to a life-threatening “diabetic coma.” Together, these complications make diabetes the seventh leading cause of death in the United States. Diabetes is diagnosed when lab tests reveal that blood glucose levels are higher than normal, a condition called **hyperglycemia**. The treatment of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. As noted earlier, moderate weight loss, regular physical activity, and consumption of a healthful diet can reduce blood glucose levels. Some patients with type 2 diabetes may be unable to control their disease with these lifestyle changes, and will require medication. Historically, the first-line treatment of type 2 diabetes was insulin. Research advances have resulted in alternative options, including medications that enhance pancreatic function.

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Visit this link to view an animation describing the role of insulin and the pancreas in diabetes.

Chapter Review

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide. Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose uptake and utilization by target cells, as well as the storage of excess glucose for later use. Dysfunction of the production of insulin or target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

Interactive Link Questions

Visit this link to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

Insulin is overproduced.

Review Questions

If an autoimmune disorder targets the alpha cells, production of which hormone would be directly affected?

1. somatostatin
2. pancreatic polypeptide
3. insulin
4. glucagon

D

Which of the following statements about insulin is true?

1. Insulin acts as a transport protein, carrying glucose across the cell membrane.
2. Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.
3. Insulin stimulates the breakdown of stored glycogen into glucose.
4. Insulin stimulates the kidneys to reabsorb glucose into the bloodstream.

B

Critical Thinking Questions

What would be the physiological consequence of a disease that destroyed the beta cells of the pancreas?

The beta cells produce the hormone insulin, which is important in the regulation of blood glucose levels. All insulin-dependent cells of the body require insulin in order to take up glucose from the bloodstream. Destruction of the beta cells would result in an inability to produce and secrete insulin, leading to abnormally high blood glucose levels and the disease called type

1 diabetes mellitus.

Why is foot care extremely important for people with diabetes mellitus?

Excessive blood glucose levels damage the blood vessels and nerves of the body’s extremities, increasing the risk for injury, infection, and tissue death. Loss of sensation to the feet means that a diabetic patient will not be able to feel foot trauma, such as from ill-fitting shoes. Even minor injuries commonly lead to infection, which , can progress to tissue death without proper care, requiring amputation.

Glossary

alpha cell
: pancreatic islet cell type that produces the hormone glucagon

beta cell
: pancreatic islet cell type that produces the hormone insulin

delta cell
: minor cell type in the pancreas that secretes the hormone somatostatin

diabetes mellitus
: condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

glucagon
: pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels

hyperglycemia
: abnormally high blood glucose levels

insulin
: pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels

pancreas
: organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood glucose

pancreatic islets
: specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans

PP cell
: minor cell type in the pancreas that secretes

the hormone pancreatic polypeptide

Introduction
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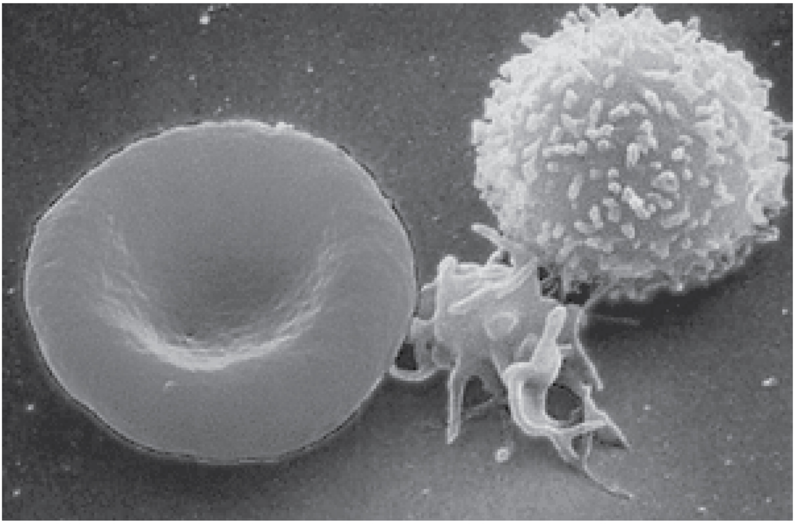
Blood Cells
A single drop of blood contains millions of red blood cells, white blood cells, and platelets. One of each type is shown here, isolated from a scanning electron micrograph.



Chapter Objectives
After studying this chapter, you will be able to:

- Identify the primary functions of blood, its fluid and cellular components, and its physical characteristics
- Identify the most important proteins and other solutes present in blood plasma
- Describe the formation of the formed element

components of blood

- Discuss the structure and function of red blood cells and hemoglobin
- Classify and characterize white blood cells
- Describe the structure of platelets and explain the process of hemostasis
- Explain the significance of AB and Rh blood groups in blood transfusions
- Discuss a variety of blood disorders

Single-celled organisms do not need blood. They obtain nutrients directly from and excrete wastes directly into their environment. The human organism cannot do that. Our large, complex bodies need blood to deliver nutrients to and remove wastes from our trillions of cells. The heart pumps blood throughout the body in a network of blood vessels. Together, these three components—blood, heart, and vessels—makes up the cardiovascular system. This chapter focuses on the medium of transport: blood.

An Overview of Blood

By the end of this section, you will be able to:

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample
- Discuss the unique physical characteristics of blood
- Identify the composition of blood plasma, including its most important solutes and plasma proteins

Recall that **blood** is a connective tissue. Like all connective tissues, it is made up of cellular elements and an extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of

the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma ([link]). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets,

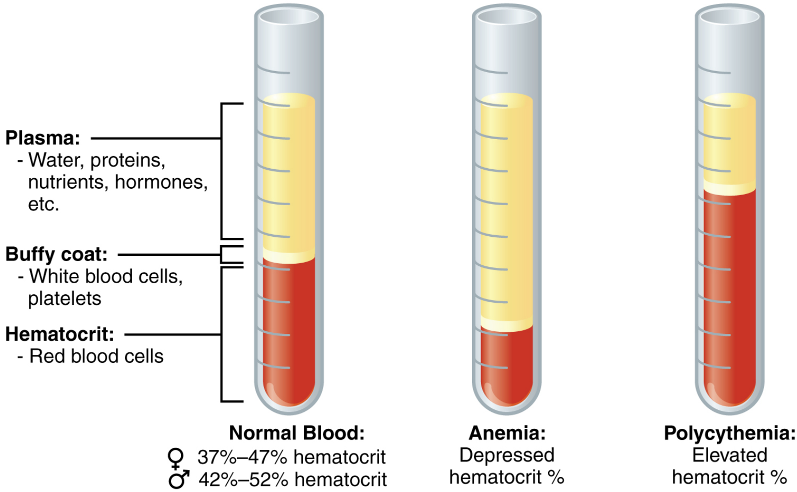
cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as **packed cell volume (PCV)**. In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

Composition of Blood

The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the

erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.



Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's

thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4–5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Visit this site for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in [link].

The three major groups of plasma proteins are as follows:

- **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.
- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta

globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.

- The least abundant plasma protein is **fibrinogen**. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids;

and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

Major Blood Components

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)—plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Career Connection

Phlebotomy and Medical Lab Technology

Phlebotomists are professionals trained to draw

blood (phleb- = “a blood vessel”; -tomy = “to cut”). When more than a few drops of blood are required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressly for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor’s degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT)

typically have an associate’s degree but may perform duties similar to those of an MT.

- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

Chapter Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water. The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Interactive Link Questions

Visit this site for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

There are values given for percent saturation, tension, and blood gas, and there are listings for different types of hemoglobin.

Review Questions

Which of the following statements about blood is true?

1. Blood is about 92 percent water.
2. Blood is slightly more acidic than water.
3. Blood is slightly more viscous than water.
4. Blood is slightly more salty than seawater.

C

Which of the following statements about albumin is true?

1. It draws water out of the blood vessels and into the body’s tissues.
2. It is the most abundant plasma protein.
3. It is produced by specialized leukocytes called plasma cells.
4. All of the above are true.

B

Which of the following plasma proteins is *not* produced by the liver?

1. fibrinogen
2. alpha globulin
3. beta globulin
4. immunoglobulin

D

Critical Thinking Questions

A patient’s hematocrit is 42 percent. Approximately what percentage of the patient’s blood is plasma?

The patient’s blood is approximately 58 percent plasma (since the buffy coat is less than 1 percent).

Why would it be incorrect to refer to the formed elements as cells?

The formed elements include erythrocytes and leukocytes, which are cells (although mature erythrocytes do not have a nucleus); however, the formed elements also include platelets, which are not true cells but cell fragments.

True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.

False. The buffy coat is the portion of blood that is made up of its leukocytes and platelets.

Glossary

albumin

most abundant plasma protein, accounting for most of the osmotic pressure of plasma

antibodies
: (also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

blood
: liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

buffy coat
: thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

fibrinogen
: plasma protein produced in the liver and involved in blood clotting

formed elements
: cellular components of blood; that is, erythrocytes, leukocytes, and platelets

globulins
: heterogeneous group of plasma proteins that

includes transport proteins, clotting factors, immune proteins, and others

hematocrit
: (also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

immunoglobulins
: (also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

packed cell volume (PCV)
: (also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood

plasma
: in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

platelets
: (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

red blood cells (RBCs)

(also, erythrocytes) one of the formed elements of blood that transports oxygen

white blood cells (WBCs)
: (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

Production of the Formed Elements
By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root haima- = “blood”; -poiesis = “production”).

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the

developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Formed Elements from Stem Cells

All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchal system, with some loss of the

ability to diversify at each step. The **totipotent stem cell** is the zygote, or fertilized egg. The totipotent (toti- = “all”) stem cell gives rise to all cells of the human body. The next level is the **pluripotent stem cell**, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hemopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hemopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hemopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more specialized stem cells ([link]):

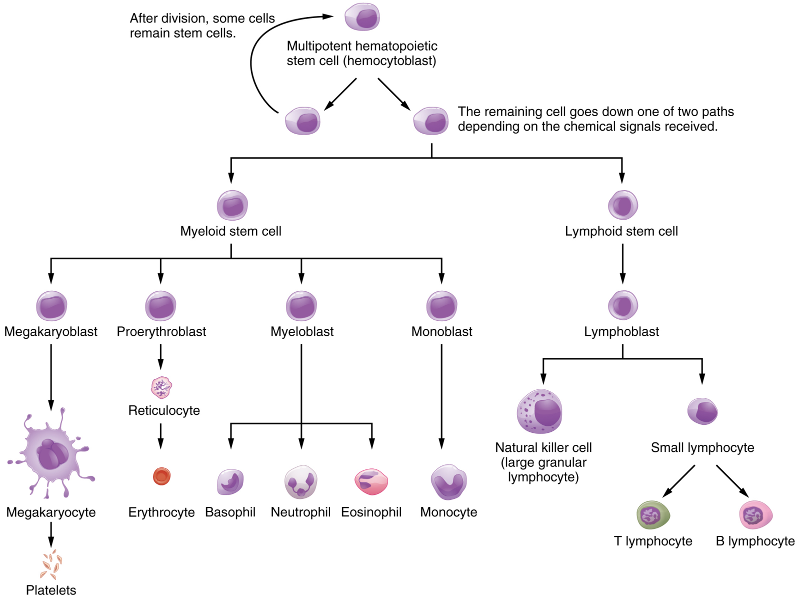
- **Lymphoid stem cells** give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently

from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.

- **Myeloid stem cells** give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.

Hematopoietic System of Bone Marrow

Hemopoiesis is the proliferation and differentiation of the formed elements of blood.



Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in [link], there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix -blast. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- **Erythropoietin (EPO)** is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain

types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.

- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.

    - **Colony-stimulating factors (CSFs)** are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms

of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.

- **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Everyday Connection

Blood Doping

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the

tissues, providing extra aerobic capacity, clinically referred to as VO_2 max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling.

Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

Watch this video to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone marrow, or a **bone marrow transplant**, a treatment in which a donor's healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of

various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (os coxae). This location was preferred, since its location close to the body surface makes it more accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

Chapter Review

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hemopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of formed elements.

Interactive Link Questions

Watch this video to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Side effects can include heart disease, stroke, pulmonary embolism, and virus transmission.

Review Questions

Which of the formed elements arise from myeloid stem cells?

1. B cells
2. natural killer cells
3. platelets
4. all of the above

C

Which of the following statements about erythropoietin is true?

1. It facilitates the proliferation and differentiation of the erythrocyte lineage.
2. It is a hormone produced by the thyroid gland.
3. It is a hemopoietic growth factor that prompts lymphoid stem cells to leave the bone marrow.
4. Both a and b are true.

A

Interleukins are associated primarily with

which of the following?

1. production of various lymphocytes
2. immune responses
3. inflammation
4. all of the above

D

Critical Thinking Questions

Myelofibrosis is a disorder in which inflammation and scar tissue formation in the bone marrow impair hemopoiesis. One sign is an enlarged spleen. Why?

When disease impairs the ability of the bone marrow to participate in hemopoiesis, extramedullary hemopoiesis begins in the patient’s liver and spleen. This causes the spleen to enlarge.

Would you expect a patient with a form of cancer called acute myelogenous leukemia to experience impaired production of erythrocytes,

or impaired production of lymphocytes? Explain your choice.

The adjective myelogenous suggests a condition originating from (generated by) myeloid cells. Acute myelogenous leukemia impairs the production of erythrocytes and other mature formed elements of the myeloid stem cell lineage. Lymphocytes arise from the lymphoid stem cell line.

Glossary

bone marrow biopsy
: diagnostic test of a sample of red bone marrow

bone marrow transplant
: treatment in which a donor's healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient

colony-stimulating factors (CSFs)
: glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)

cytokines
: class of proteins that act as autocrine or

paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

erythropoietin (EPO)
: glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels

hemocytoblast
: hemopoietic stem cell that gives rise to the formed elements of blood

hemopoiesis
: production of the formed elements of blood

hemopoietic growth factors
: chemical signals including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins that regulate the differentiation and proliferation of particular blood progenitor cells

hemopoietic stem cell
: type of pluripotent stem cell that gives rise to the formed elements of blood (hemocytoblast)

interleukins
: signaling molecules that may function in hemopoiesis, inflammation, and specific

immune responses

lymphoid stem cells
: type of hemopoietic stem cells that gives rise to lymphocytes, including various T cells, B cells, and NK cells, all of which function in immunity

myeloid stem cells
: type of hemopoietic stem cell that gives rise to some formed elements, including erythrocytes, megakaryocytes that produce platelets, and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes (neutrophils, eosinophils, and basophils)

pluripotent stem cell
: stem cell that derives from totipotent stem cells and is capable of differentiating into many, but not all, cell types

totipotent stem cell
: embryonic stem cell that is capable of differentiating into any and all cells of the body; enabling the full development of an organism

thrombopoietin
: hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)

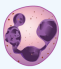
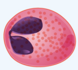
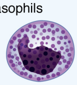
Erythrocytes

By the end of this section, you will be able to:

- Describe the anatomy of erythrocytes
- Discuss the various steps in the lifecycle of an erythrocyte
- Explain the composition and function of hemoglobin

The **erythrocyte**, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (μL) of blood, and females have approximately 4.8 million per μL. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (μm) ([link]). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body's tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

Summary of Formed Elements in Blood

Formed element	Major subtypes	Numbers present per microliter (μL) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells) 		5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	4150 (1800–7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
	Basophils 	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes 	2185 (1500–4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets 		350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

Shape and Structure of Erythrocytes

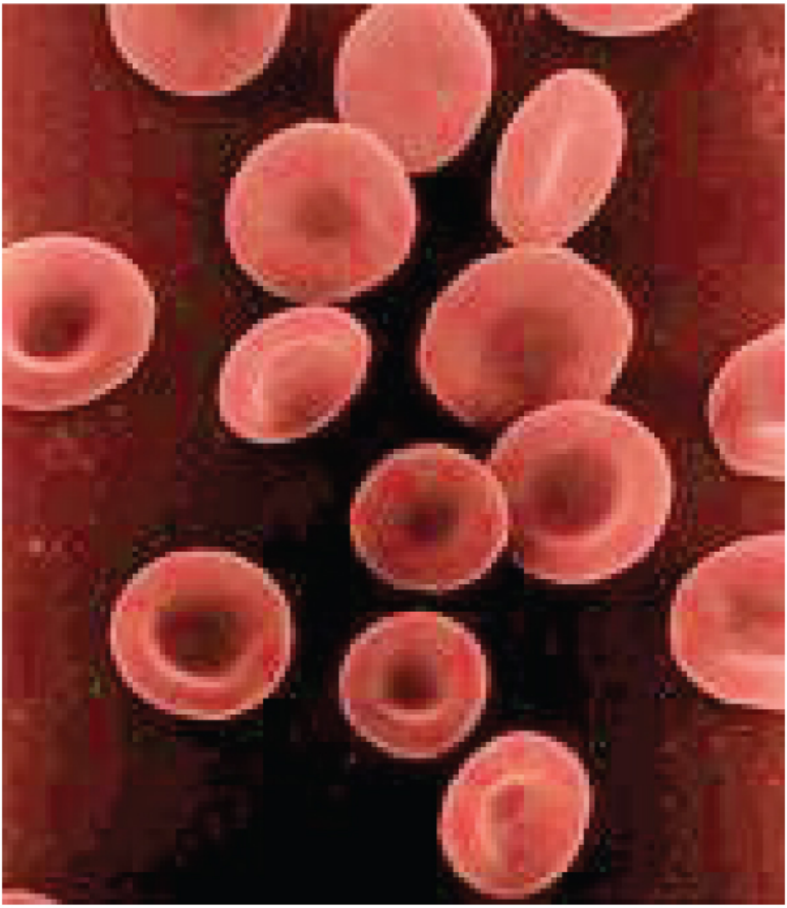
As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a **reticulocyte**, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. These remnants, primarily of networks (reticulum) of ribosomes, are quickly shed, however, and mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center ([link]). Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a

greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux, from the French word for "roll."

Shape of Red Blood Cells

Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.



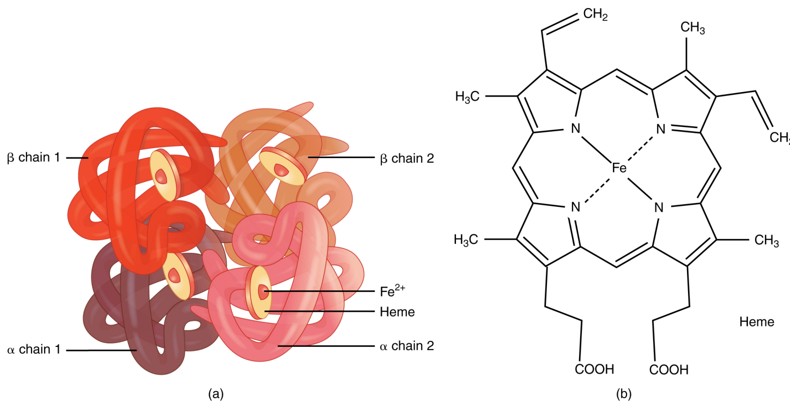
Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called **globin**, designated alpha 1 and 2, and beta 1 and 2 ([link]**a**). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron (Fe^{2+})

([link]**b**).

Hemoglobin

(a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.



Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see [link]**b**).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red

deoxyhemoglobin, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO_2, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of

hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect **hypoxemia**, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO_2 and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve

as ideal sites for receptors that determine oxygen saturation. In response to hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the summit.

Lifecycle of Erythrocytes

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second. For this production to occur, a number of raw materials must be present in adequate amounts. These include the same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino acids. However, erythrocyte production also requires several trace elements:

- Iron. We have said that each heme group in a hemoglobin molecule contains an ion of the trace mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron, from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods. Upon absorption, iron becomes part of the body’s total iron pool. The bone marrow, liver, and spleen can store iron in the protein compounds **ferritin** and **hemosiderin**. Ferroportin transports the iron across the intestinal cell plasma membranes and from its storage sites into tissue fluid where it enters the blood. When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.

- Copper. A trace mineral, copper is a component of two plasma proteins, hephaestin and ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper. Both enable the oxidation of iron from Fe^{2+} to Fe^{3+}, a form in which it can be bound to its transport protein, **transferrin**, for transport to body cells. In a state of copper deficiency, the transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can eventually lead to organ damage.
- Zinc. The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme portion of hemoglobin.
- B vitamins. The B vitamins folate and vitamin B_{12} function as co-enzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of myeloid phagocytic cell called a **macrophage**, located primarily within the bone marrow, liver, and spleen. The components of the degraded erythrocytes' hemoglobin are further processed as follows:

- Globin, the protein portion of hemoglobin, is

broken down into amino acids, which can be sent back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed from circulation by the kidneys.

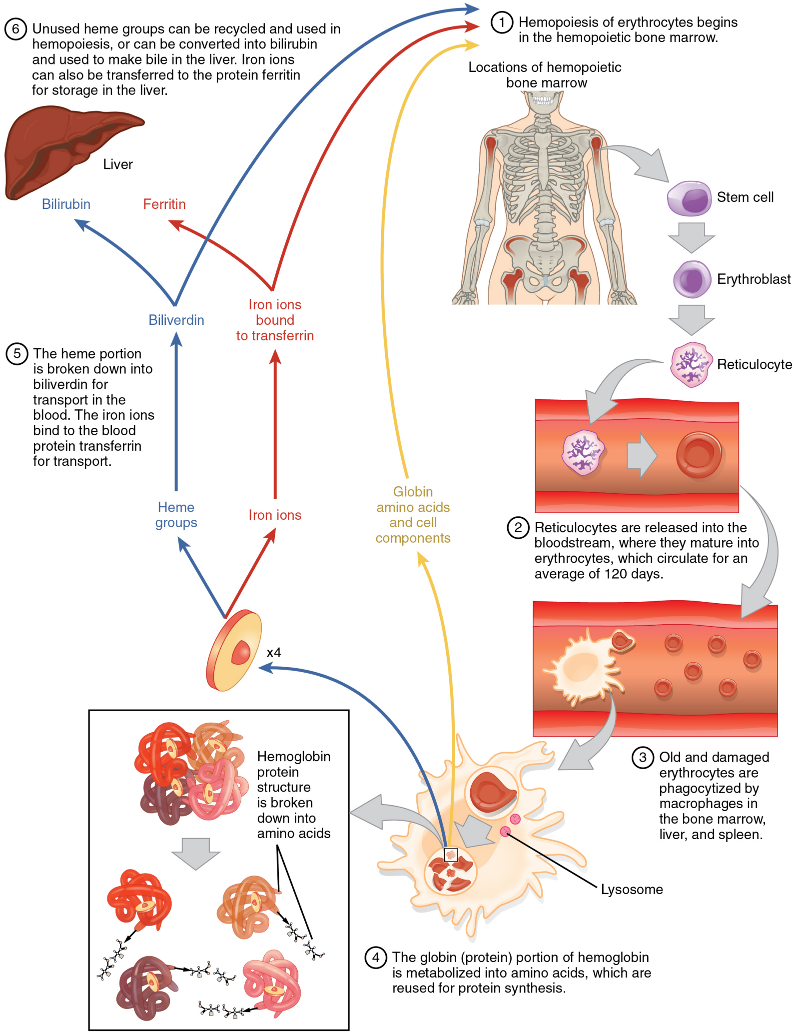
- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen, primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.
- The non-iron portion of heme is degraded into the waste product **biliverdin**, a green pigment, and then into another waste product, **bilirubin**, a yellow pigment. Bilirubin binds to albumin and travels in the blood to the liver, which uses it in the manufacture of bile, a compound released into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with bruising. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized in [link].

Erythrocyte Lifecycle

Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by macrophages, and their components are recycled.



Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health. When the number of RBCs or hemoglobin is deficient, the

general condition is called **anemia**. There are more than 400 types of anemia and more than 3.5 million Americans suffer from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In

addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in **sickle cell disease** (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations ([link]). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents

(strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.

Sickle Cells

Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet and is especially common in teens and children as well as in vegans and vegetarians. Additionally, iron deficiency anemia may be caused by either an inability to absorb and transport iron or slow, chronic bleeding.
- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.

    - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients. Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
    - Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn's disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS.
    - Pregnancies, some medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to

provide sufficient folic acid during the early stages of pregnancy to reduce the risk of neurological defects, including spina bifida, a failure of the neural tube to close.

- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.

    - Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection.
    - **Thalassemia** is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley’s anemia.
    - Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.

- Various disease processes also can lead to

anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, some forms of cancer, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called **polycythemia** and is detected in a patient's elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek vera = "true") causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than women, and is more likely to be present in elderly patients those over 60 years of age.

Chapter Review

The most abundant formed elements in blood, erythrocytes are red, biconcave disks packed with

an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs. Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Review Questions

Which of the following statements about mature, circulating erythrocytes is true?

1. They have no nucleus.

2. They are packed with mitochondria.
3. They survive for an average of 4 days.
4. All of the above

A

A molecule of hemoglobin _____.

1. is shaped like a biconcave disk packed almost entirely with iron
2. contains four glycoprotein units studded with oxygen
3. consists of four globin proteins, each bound to a molecule of heme
4. can carry up to 120 molecules of oxygen

C

The production of healthy erythrocytes depends upon the availability of _____.

1. copper
2. zinc
3. vitamin B_{12}
4. copper, zinc, and vitamin B_{12}

D

Aging and damaged erythrocytes are removed from the circulation by _____.

1. myeoblasts
2. monocytes
3. macrophages
4. mast cells

C

A patient has been suffering for 2 months with a chronic, watery diarrhea. A blood test is likely to reveal _____.

1. a hematocrit below 30 percent
2. hypoxemia
3. anemia
4. polycythemia

D

Critical Thinking Questions

A young woman has been experiencing unusually heavy menstrual bleeding for several

years. She follows a strict vegan diet (no animal foods). She is at risk for what disorder, and why?

She is at risk for anemia, because her unusually heavy menstrual bleeding results in excessive loss of erythrocytes each month. At the same time, her vegan diet means that she does not have dietary sources of heme iron. The non-heme iron she consumes in plant foods is not as well absorbed as heme iron.

A patient has thalassemia, a genetic disorder characterized by abnormal synthesis of globin proteins and excessive destruction of erythrocytes. This patient is jaundiced and is found to have an excessive level of bilirubin in his blood. Explain the connection.

Bilirubin is a breakdown product of the non-iron component of heme, which is cleaved from globin when erythrocytes are degraded. Excessive erythrocyte destruction would deposit excessive bilirubin in the blood. Bilirubin is a yellowish pigment, and high blood levels can manifest as yellowed skin.

Glossary

anemia
: deficiency of red blood cells or hemoglobin

bilirubin
: yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

biliverdin
: green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver

carbaminohemoglobin
: compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

deoxyhemoglobin
: molecule of hemoglobin without an oxygen molecule bound to it

erythrocyte
: (also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

ferritin
: protein-containing storage form of iron found in the bone marrow, liver, and spleen

globin
: heme-containing globular protein that is a constituent of hemoglobin

heme
: red, iron-containing pigment to which oxygen binds in hemoglobin

hemoglobin
: oxygen-carrying compound in erythrocytes

hemosiderin
: protein-containing storage form of iron found in the bone marrow, liver, and spleen

hypoxemia
: below-normal level of oxygen saturation of blood (typically <95 percent)

macrophage
: phagocytic cell of the myeloid lineage; a matured monocyte

oxyhemoglobin
: molecule of hemoglobin to which oxygen is bound

polycythemia
: elevated level of hemoglobin, whether adaptive or pathological

reticulocyte
: immature erythrocyte that may still contain

fragments of organelles

sickle cell disease
: (also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

thalassemia
: inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

transferrin
: plasma protein that binds reversibly to iron and distributes it throughout the body

Leukocytes and Platelets

By the end of this section, you will be able to:

- Describe the general characteristics of leukocytes
- Classify leukocytes according to their lineage, their main structural features, and their primary functions
- Discuss the most common malignancies involving leukocytes
- Identify the lineage, basic structure, and function of platelets

The **leukocyte**, commonly known as a white blood cell (or WBC), is a major component of the body's defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA, and they clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair. See [link] for a summary of leukocytes and platelets.

Characteristics of Leukocytes

Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less

numerous than erythrocytes: Typically there are only 5000 to 10,000 per μL. They are also larger than erythrocytes and are the only formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

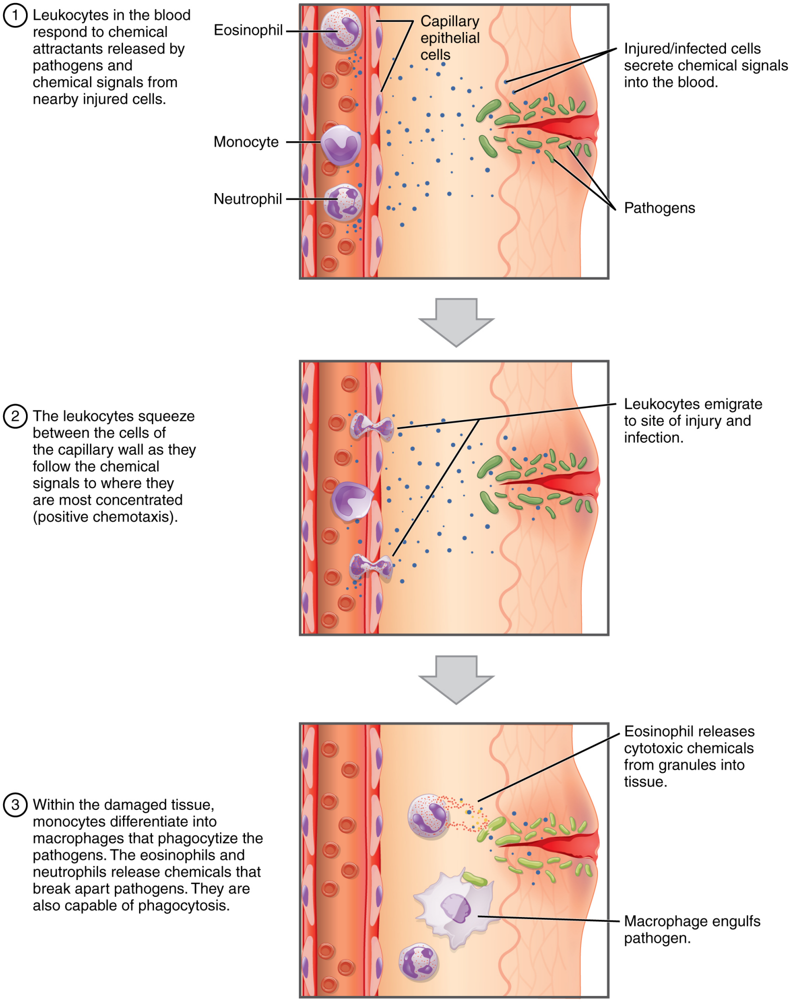
One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in [link], they leave the capillaries—the smallest blood vessels—or other small vessels through a process known as **emigration** (from the Latin for "removal") or **diapedesis** (dia- = "through"; -pedan = "to leap") in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or

other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally "movement in response to chemicals"), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical "911" call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.

Emigration

Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound. Some leukocytes, such as the eosinophil and neutrophil, are characterized as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.



Classification of Leukocytes

When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible

granules:

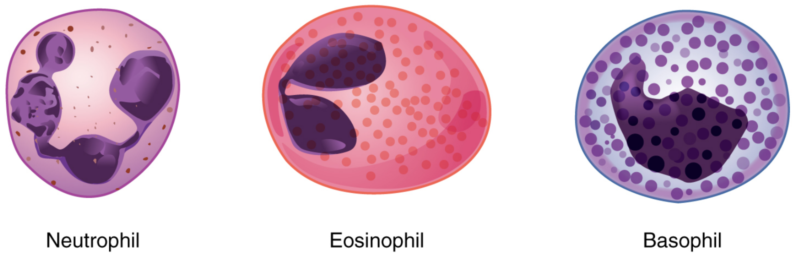
- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in [link]).
- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules ([link]).

Granular Leukocytes

A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil’s granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.



The most common of all the leukocytes, **neutrophils** will normally comprise 50–70 percent of total leukocyte count. They are 10–12 μm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as **polymorphonuclear** (a nucleus with many forms), or simply "polys." Younger and immature neutrophils begin to develop lobes and are known as "bands."

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include **lysozyme**, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and **defensins**, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out.

Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 μm in diameter. The granules of eosinophils stain best with an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations,

and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.

Agranular Leukocytes

Agranular leukocytes contain smaller, less-visible granules in their cytoplasm than do granular

leukocytes. The nucleus is simple in shape, sometimes with an indentation but without distinct lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see [link]).

Lymphocytes are the only formed element of blood that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are 10–14 μm and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 μm with a larger volume of nucleus to cytoplasm, creating a "halo" effect. A few cells may fall outside these ranges, at 14–17 μm. This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. **Natural killer (NK) cells** are capable of recognizing cells that do not express "self" proteins on their plasma membrane or that contain foreign or abnormal markers. These "nonself" cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide

generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called **B lymphocytes** and **T lymphocytes**, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. T cells provide cellular-level immunity by physically attacking foreign or diseased cells. A **memory cell** is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the bone marrow, whereas T cells undergo maturation in the thymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or

immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

Monocytes originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of 12–20 μm and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation and phagocytize debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

Lifecycle of Leukocytes

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the

influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see [link]) and are large, typically 50–100 μm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue ([link]) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These enclosed

fragments are platelets. Each megakarocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

Platelets are relatively small, 2–4 μm in diameter, but numerous, with typically 150,000–160,000 per μL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

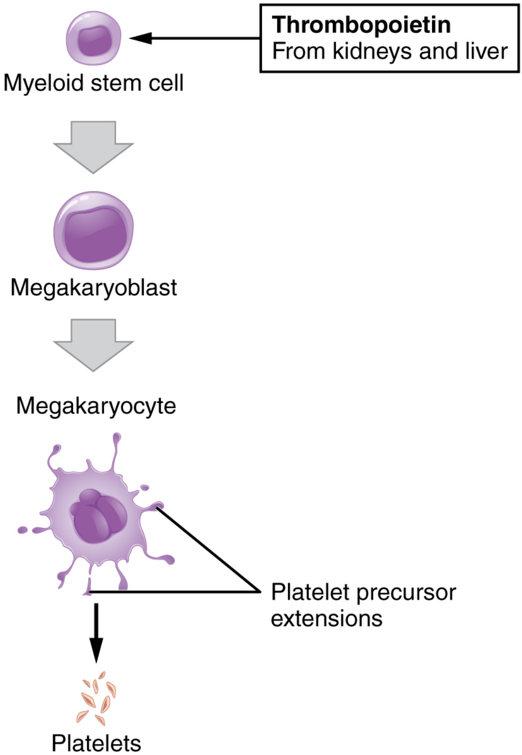
Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called **thrombocytopenia**, blood may not

clot properly, and excessive bleeding may result.

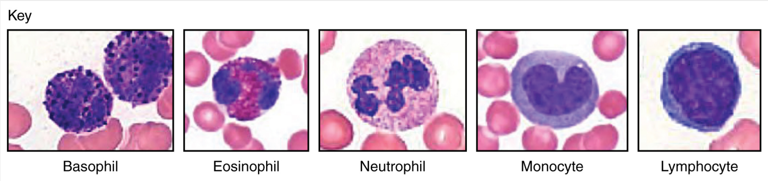
Platelets

Platelets are derived from cells called megakaryocytes.



Leukocytes

(Micrographs provided by the Regents of University of Michigan Medical School © 2012)



View University of Michigan Webscopes at http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/081-2_HISTO_40X.svs/view.apml?cwidth=860&cheight=733&chost=virtualslides.med.umi and explore the blood slides in greater detail. The Webscope feature allows you to move the slides as you would with a mechanical stage. You can increase and decrease the magnification. There is a chance to review each of the leukocytes individually after you have attempted to identify them from the first two blood smears. In addition, there are a few multiple choice questions.

Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to

be abnormal?

Chapter Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the body's defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Interactive Link Questions

[link] Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

[link] This should appear to be a normal blood smear.

Review Questions

The process by which leukocytes squeeze through adjacent cells in a blood vessel wall is

called _____.

1. leukocytosis
2. positive chemotaxis
3. emigration
4. cytoplasmic extending

C

Which of the following describes a neutrophil?

1. abundant, agranular, especially effective against cancer cells
2. abundant, granular, especially effective against bacteria
3. rare, agranular, releases antimicrobial defensins
4. rare, granular, contains multiple granules packed with histamine

---

B

T and B lymphocytes _____.

1. are polymorphonuclear
2. are involved with specific immune function
3. proliferate excessively in leukopenia

4. are most active against parasitic worms

B

A patient has been experiencing severe, persistent allergy symptoms that are reduced when she takes an antihistamine. Before the treatment, this patient was likely to have had increased activity of which leukocyte?

1. basophils
2. neutrophils
3. monocytes
4. natural killer cells

A

Thrombocytes are more accurately called _____.

1. clotting factors
2. megakaryoblasts
3. megakaryocytes
4. platelets

D

Critical Thinking Questions

One of the more common adverse effects of cancer chemotherapy is the destruction of leukocytes. Before his next scheduled chemotherapy treatment, a patient undergoes a blood test called an absolute neutrophil count (ANC), which reveals that his neutrophil count is 1900 cells per microliter. Would his healthcare team be likely to proceed with his chemotherapy treatment? Why?

A neutrophil count below 1800 cells per microliter is considered abnormal. Thus, this patient's ANC is at the low end of the normal range and there would be no reason to delay chemotherapy. In clinical practice, most patients are given chemotherapy if their ANC is above 1000.

A patient was admitted to the burn unit the previous evening suffering from a severe burn involving his left upper extremity and shoulder. A blood test reveals that he is experiencing leukocytosis. Why is this an expected finding?

Any severe stress can increase the leukocyte

count, resulting in leukocytosis. A burn is especially likely to increase the proliferation of leukocytes in order to ward off infection, a significant risk when the barrier function of the skin is destroyed.

Glossary

agranular leukocytes
: leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

B lymphocytes
: (also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

basophils
: granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

defensins
: antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

diapedesis
: (also, emigration) process by which leukocytes squeeze through adjacent cells in a

blood vessel wall to enter tissues

emigration
: (also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

eosinophils
: granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

granular leukocytes
: leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils

leukemia
: cancer involving leukocytes

leukocyte
: (also, white blood cell) colorless, nucleated blood cell, the chief function of which is to protect the body from disease

leukocytosis
: excessive leukocyte proliferation

leukopenia
: below-normal production of leukocytes

lymphocytes
: agranular leukocytes of the lymphoid stem

cell line, many of which function in specific immunity

lymphoma
: form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues

lysozyme
: digestive enzyme with bactericidal properties

megakaryocyte
: bone marrow cell that produces platelets

memory cell
: type of B or T lymphocyte that forms after exposure to a pathogen

monocytes
: agranular leukocytes of the myeloid stem cell line that circulate in the bloodstream; tissue monocytes are macrophages

natural killer (NK) cells
: cytotoxic lymphocytes capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers; provide generalized, nonspecific immunity

neutrophils
: granulocytes that stain with a neutral dye and

are the most numerous of the leukocytes; especially active against bacteria

polymorphonuclear
: having a lobed nucleus, as seen in some leukocytes

positive chemotaxis
: process in which a cell is attracted to move in the direction of chemical stimuli

T lymphocytes
: (also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thrombocytes
: platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia
: condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis
: condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

Blood Typing

By the end of this section, you will be able to:

- Describe the two basic physiological consequences of transfusion of incompatible blood
- Compare and contrast ABO and Rh blood groups
- Identify which blood groups may be safely transfused into patients with different ABO types
- Discuss the pathophysiology of hemolytic disease of the newborn

Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient’s own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

Antigens, Antibodies, and Transfusion Reactions

Antigens are substances that the body does not recognize as belonging to the "self" and that therefore trigger a defensive response from the leukocytes of the immune system. (Seek more content for additional information on immunity.) Here, we will focus on the role of immunity in blood transfusion reactions. With RBCs in particular, you may see the antigens referred to as isoantigens or agglutinogens (surface antigens) and the antibodies referred to as isoantibodies or agglutinins. In this chapter, we will use the more common terms antigens and antibodies.

Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following an infusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the infused erythrocytes and cause them to adhere to one another.

- Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of

erythrocytes. This process is called **agglutination**.
- The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.
- As the erythrocyte clumps are degraded, in a process called **hemolysis**, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney's capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on

their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have

been identified, only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh+) and those who lack it are Rh negative (Rh−). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient's blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A+) means ABO group A blood with the Rh antigen present, and AB negative (AB−) means ABO group AB blood without the Rh antigen.

[link] summarizes the distribution of the ABO and Rh blood types within the United States.

Summary of ABO and Rh Blood Types within the United States

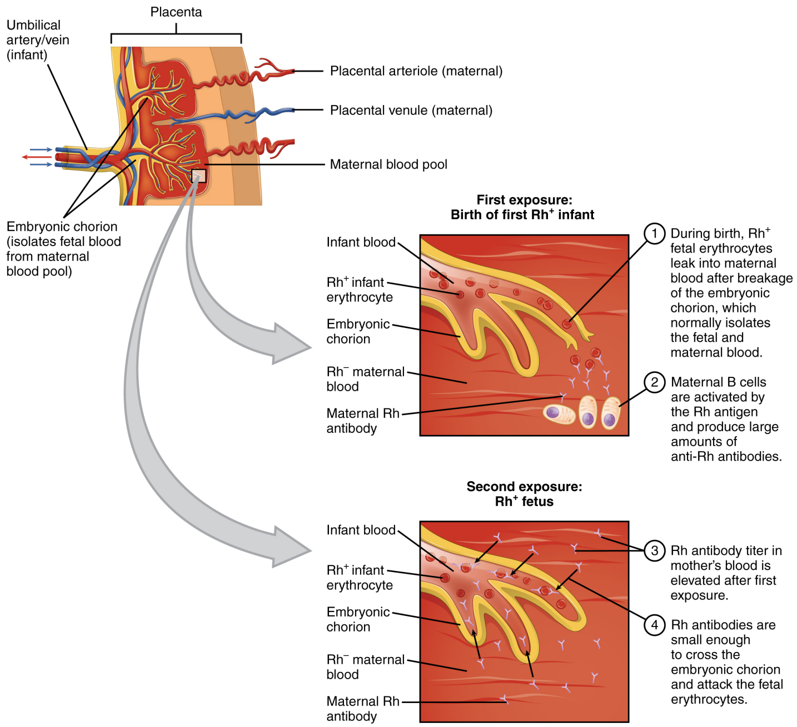
Blood Type	African-Americans	Asian-Americans	Caucasian-Americans	Latino/Latina-Americans
A+	24	27	33	29
A−	2	0.5	7	2
B+	18	25	9	9
B−	1	0.4	2	1
AB+	4	7	3	2
AB−	0.3	0.1	1	0.2
O+	47	39	37	53
O−	4	1	8	4

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh− individuals after exposure to the antigen. This process, called sensitization, occurs following a transfusion with Rh-incompatible blood or, more commonly, with the birth of an Rh+ baby to an Rh− mother. Problems are rare in a first pregnancy, since the baby's Rh+ cells rarely cross the placenta (the organ of gas and nutrient exchange between the baby and the mother). However, during or immediately after birth, the Rh− mother can be exposed to the baby's Rh+ cells ([link]). Research has shown that this occurs in about 13−14 percent of such pregnancies. After exposure, the mother's immune system begins to generate anti-Rh antibodies. If the mother should then conceive another Rh+ baby, the Rh antibodies she has produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This

condition, known as **hemolytic disease of the newborn (HDN)** or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

Erythroblastosis Fetalis

The first exposure of an Rh− mother to Rh+ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to circulate in the mother's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh+ fetus in the uterus. Maternal anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.



A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh$-$ mother, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh$+$ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh$-$ mothers during weeks $26-28$ of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh$+$ subsequent pregnancy to an Rh$-$ mother is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

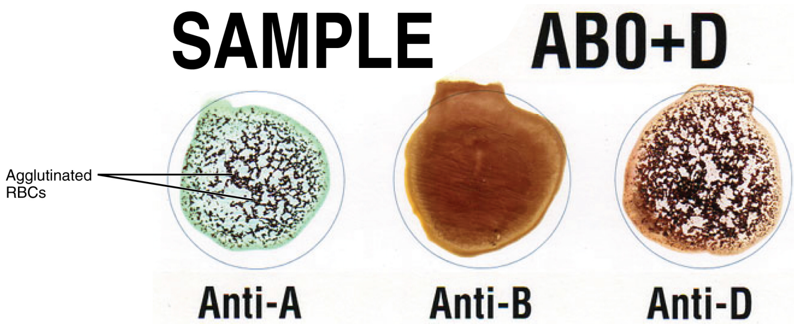
Determining ABO Blood Types

Clinicians are able to determine a patient's blood type quickly and easily using commercially prepared antibodies. An unknown blood sample is allocated into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells ([link]). The blood should also be tested for Rh antibodies.

Cross Matching Blood Types

This sample of a commercially produced "bedside"

card enables quick typing of both a recipient's and donor's blood before transfusion. The card contains three reaction sites or wells. One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called anti-seras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A+. For the purpose of transfusion, the donor's and recipient's blood types must match.



ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B+ recipient should ideally receive blood only from a type B+ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient's life, there may not be time for cross

matching to identify blood type. In these cases, blood from a **universal donor**—an individual with type O− blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient's blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O− individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient's own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh− individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient's blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB+ is known as the

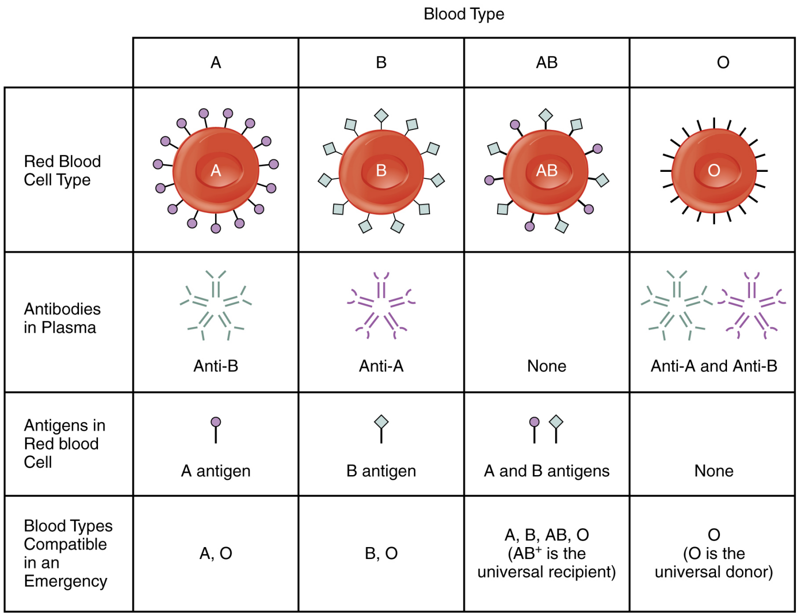
universal recipient. This patient can theoretically receive any type of blood, because the patient's own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh+ patient can receive both Rh+ and Rh− blood. However, keep in mind that the donor's blood will contain circulating antibodies, again with possible negative implications. [link] summarizes the blood types and compatibilities.

At the scene of multiple-vehicle accidents, military engagements, and natural or human-caused disasters, many victims may suffer simultaneously from acute hemorrhage, yet type O blood may not be immediately available. In these circumstances, medics may at least try to replace some of the volume of blood that has been lost. This is done by intravenous administration of a saline solution that provides fluids and electrolytes in proportions equivalent to those of normal blood plasma. Research is ongoing to develop a safe and effective artificial blood that would carry out the oxygen-carrying function of blood without the RBCs, enabling transfusions in the field without concern for incompatibility. These blood substitutes normally contain hemoglobin- as well as perfluorocarbon-based oxygen carriers.

ABO Blood Group

This chart summarizes the characteristics of the blood types in the ABO blood group. See the text for

more on the concept of a universal donor or recipient.



Chapter Review

Antigens are nonself molecules, usually large proteins, which provoke an immune response. In transfusion reactions, antibodies attach to antigens on the surfaces of erythrocytes and cause agglutination and hemolysis. ABO blood group antigens are designated A and B. People with type A blood have A antigens on their erythrocytes, whereas those with type B blood have B antigens. Those with AB blood have both A and B antigens, and those with type O blood have neither A nor B antigens. The blood plasma contains preformed

antibodies against the antigens not present on a person's erythrocytes.

A second group of blood antigens is the Rh group, the most important of which is Rh D. People with Rh− blood do not have this antigen on their erythrocytes, whereas those who are Rh+ do. About 85 percent of Americans are Rh+. When a woman who is Rh− becomes pregnant with an Rh+ fetus, her body may begin to produce anti-Rh antibodies. If she subsequently becomes pregnant with a second Rh+ fetus and is not treated preventively with RhoGAM, the fetus will be at risk for an antigen-antibody reaction, including agglutination and hemolysis. This is known as hemolytic disease of the newborn.

Cross matching to determine blood type is necessary before transfusing blood, unless the patient is experiencing hemorrhage that is an immediate threat to life, in which case type O− blood may be transfused.

Review Questions

The process in which antibodies attach to antigens, causing the formation of masses of linked cells, is called _____.

1. sensitization
2. coagulation
3. agglutination
4. hemolysis

C

People with ABO blood type O _____.

1. have both antigens A and B on their erythrocytes
2. lack both antigens A and B on their erythrocytes
3. have neither anti-A nor anti-B antibodies circulating in their blood plasma
4. are considered universal recipients

B

Hemolytic disease of the newborn is a risk during a subsequent pregnancy in which _____.

1. a type AB mother is carrying a type O fetus
2. a type O mother is carrying a type AB fetus
3. an Rh+ mother is carrying an Rh− fetus
4. an Rh− mother is carrying a second Rh+ fetus

D

Critical Thinking Questions

Following a motor vehicle accident, a patient is rushed to the emergency department with multiple traumatic injuries, causing severe bleeding. The patient's condition is critical, and there is no time for determining his blood type. What type of blood is transfused, and why?

In emergency situations, blood type O− will be infused until cross matching can be done. Blood type O− is called the universal donor blood because the erythrocytes have neither A nor B antigens on their surface, and the Rh factor is negative.

In preparation for a scheduled surgery, a patient visits the hospital lab for a blood draw. The technician collects a blood sample and performs a test to determine its type. She places a sample of the patient's blood in two wells. To the first well she adds anti-A antibody. To the second she adds anti-B antibody. Both samples visibly agglutinate. Has the technician made an

error, or is this a normal response? If normal, what blood type does this indicate?

The lab technician has not made an error. Blood type AB has both A and B surface antigens, and neither anti-A nor anti-B antibodies circulating in the plasma. When anti-A antibodies (added to the first well) contact A antigens on AB erythrocytes, they will cause agglutination. Similarly, when anti-B antibodies contact B antigens on AB erythrocytes, they will cause agglutination.

References

American Red Cross (US). Blood types [Internet]. c2013 [cited 2013 Apr 3]. Available from: http://www.redcrossblood.org/learn-about-blood/blood-types 2013

Glossary

ABO blood group
: blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination

clustering of cells into masses linked by antibodies

cross matching
: blood test for identification of blood type using antibodies and small samples of blood

hemolysis
: destruction (lysis) of erythrocytes and the release of their hemoglobin into circulation

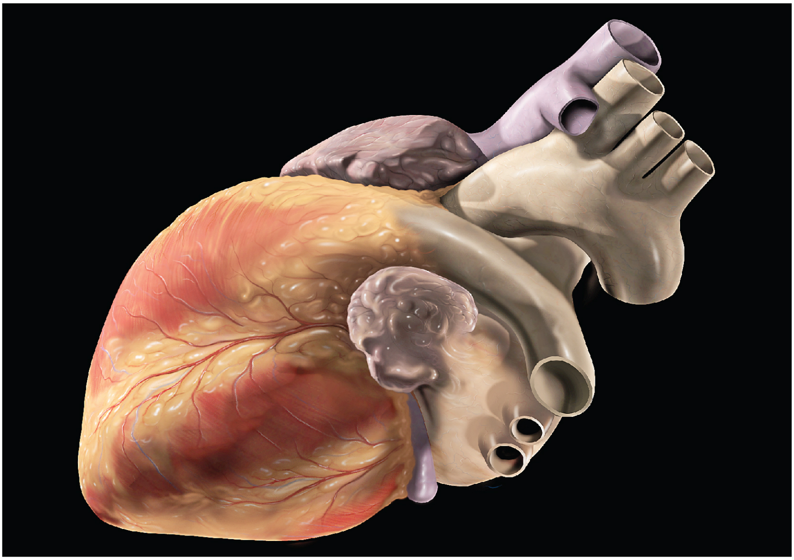
hemolytic disease of the newborn (HDN)
: (also, erythroblastosis fetalis) disorder causing agglutination and hemolysis in an Rh$+$ fetus or newborn of an Rh$-$ mother

Rh blood group
: blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

universal donor
: individual with type O$-$ blood

universal recipient
: individual with type AB$+$ blood

Introduction
class="introduction"
Human Heart
This artist’s conception of the human heart suggests a powerful engine—not inappropriate for a muscular pump that keeps the body continually supplied with blood. (credit: Patrick J. Lynch)



Chapter Objectives
After studying this chapter, you will be able to:

- Identify and describe the interior and exterior parts of the human heart
- Describe the path of blood through the cardiac circuits
- Describe the size, shape, and location of the

heart
- Compare cardiac muscle to skeletal and smooth muscle
- Explain the cardiac conduction system
- Describe the process and purpose of an electrocardiogram
- Explain the cardiac cycle
- Calculate cardiac output
- Describe the effects of exercise on cardiac output and heart rate
- Name the centers of the brain that control heart rate and describe their function
- Identify other factors affecting heart rate
- Describe fetal heart development

In this chapter, you will explore the remarkable pump that propels the blood into the vessels. There is no single better word to describe the function of the heart other than “pump,” since its contraction develops the pressure that ejects blood into the major vessels: the aorta and pulmonary trunk. From these vessels, the blood is distributed to the remainder of the body. Although the connotation of the term “pump” suggests a mechanical device made of steel and plastic, the anatomical structure is a living, sophisticated muscle. As you read this chapter, try to keep these twin concepts in mind: pump and muscle.

Although the term "heart" is an English word, cardiac (heart-related) terminology can be traced back to the Latin term, "kardia." Cardiology is the study of the heart, and cardiologists are the physicians who deal primarily with the heart.

Heart Anatomy

By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity
- Describe the internal and external anatomy of the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Compare systemic circulation to pulmonary circulation
- Identify the veins and arteries of the coronary circulation system
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart

The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In

order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

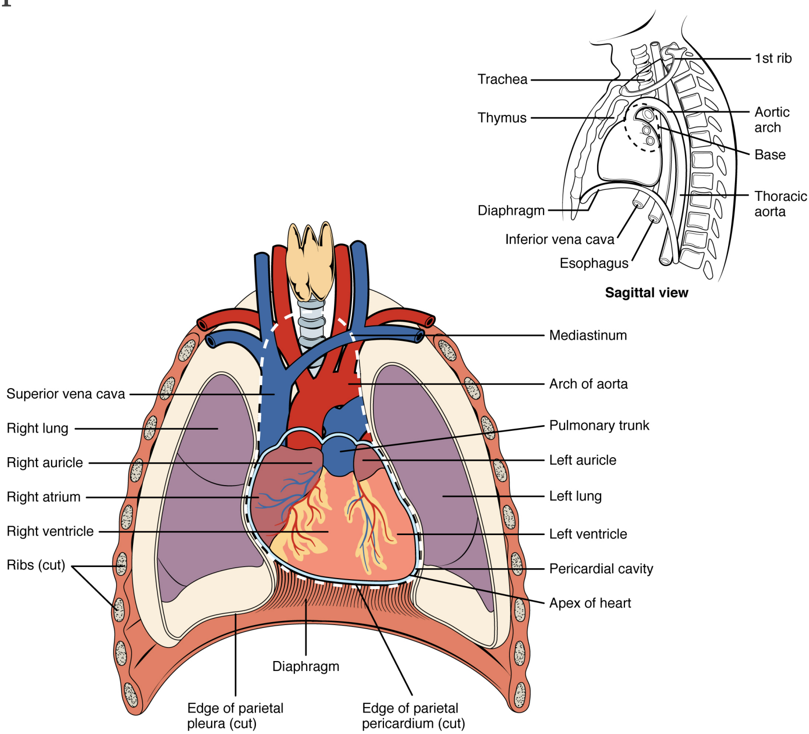
Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. [link] shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in [link]. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart

sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.

Position of the Heart in the Thorax

The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.



Everyday Connection

CPR

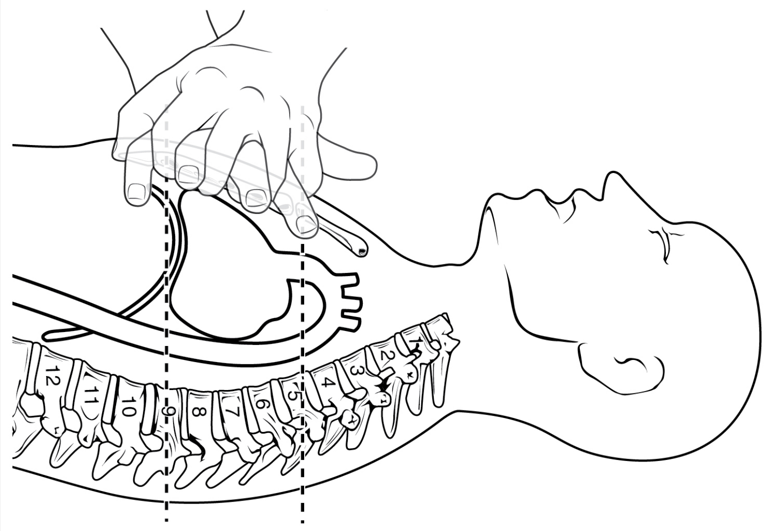
The position of the heart in the torso between the vertebrae and sternum (see [link] for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the line at T4 and T9 ([link]), it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in “Staying Alive,” recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a

consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

CPR Technique

If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.



Visit the American Heart Association website to help locate a course near your home in the United States. There are also many other national and regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex (see [link]). A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in

aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

There are two distinct but linked circuits in the

human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **systemic circuit** transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the **pulmonary trunk**, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries**. These vessels in turn branch many times before reaching the **pulmonary capillaries**, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the **pulmonary veins**—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many

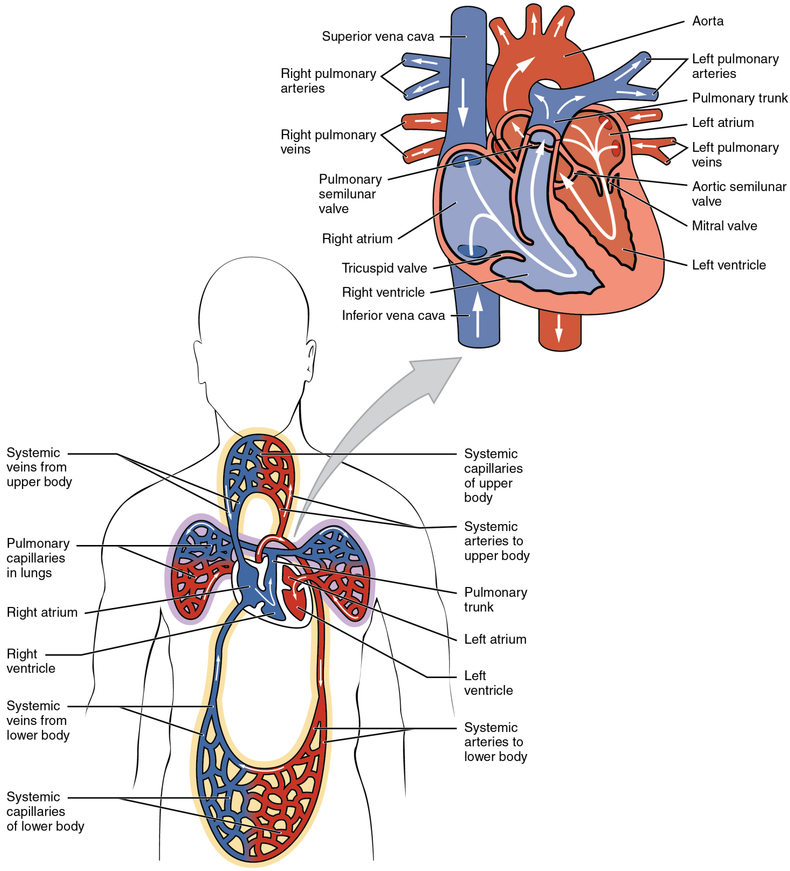
branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the **superior vena cava** and the **inferior vena cava**, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions ([link]).

Dual System of the Human Blood Circulation

Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here,

blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.



Membranes, Surface Features, and Layers

Our exploration of more in-depth heart structures begins by examining the membrane that surrounds

the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

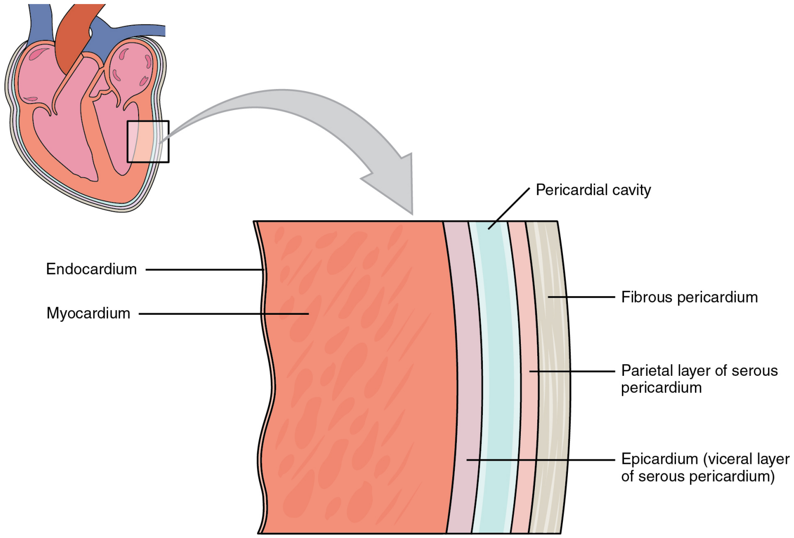
The membrane that directly surrounds the heart and defines the pericardial cavity is called the **pericardium** or **pericardial sac**. It also surrounds the "roots" of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as "around the heart," consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a

mesothelium, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. [link] illustrates the pericardial membrane and the layers of the heart.

Pericardial Membranes and Layers of the Heart Wall

The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.



Disorders of the…

Heart: Cardiac Tamponade

If excess fluid builds within the pericardial space, it

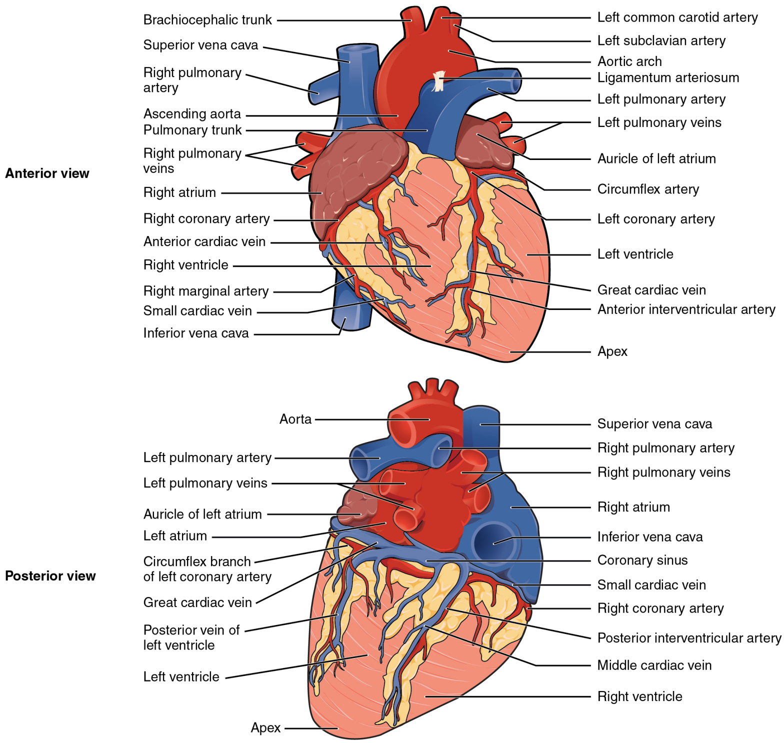
can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an **auricle**—a name that means “ear like”—because its shape resembles the external ear of a human ([link]). Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a **sulcus** (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep **coronary sulcus** is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The **anterior interventricular sulcus** is visible on the anterior surface of the heart, whereas the **posterior interventricular sulcus** is visible on the posterior surface of the heart. [link] illustrates anterior and posterior views of the surface of the heart.

External Anatomy of the Heart

Inside the pericardium, the surface features of the heart are visible.



Layers

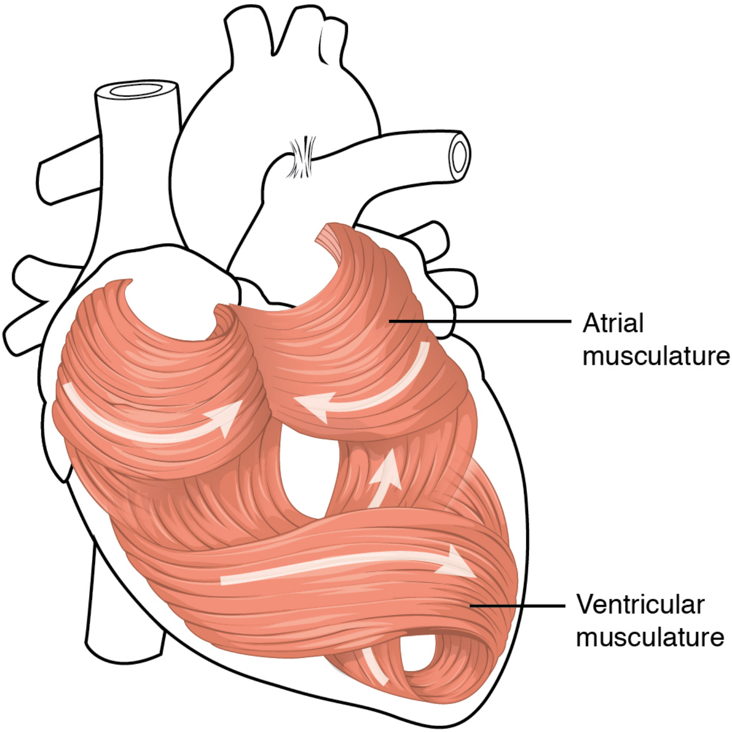
The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see [link]). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood

vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. [link] illustrates the arrangement of muscle cells.

Heart Musculature

The swirling pattern of cardiac muscle tissue contributes significantly to the heart’s ability to pump blood effectively.

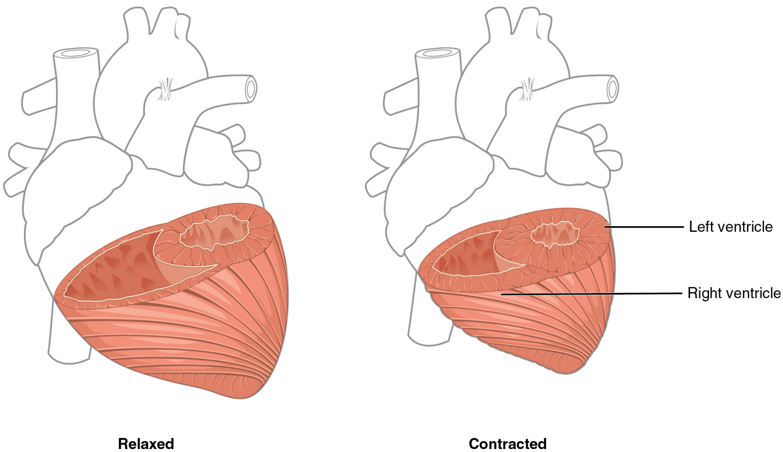


Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. [link] illustrates the differences in muscular thickness needed for each of the ventricles.

Differences in Ventricular Muscle Thickness

The myocardium in the left ventricle is significantly

thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.



The innermost layer of the heart wall, the **endocardium**, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels (see [link]).

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play

active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

The word septum is derived from the Latin for "something that encloses;" in this case, a **septum** (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the

interatrial septum. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the **fossa ovalis**, a remnant of an opening in the fetal heart known as the **foramen ovale**. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the **septum primum** that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

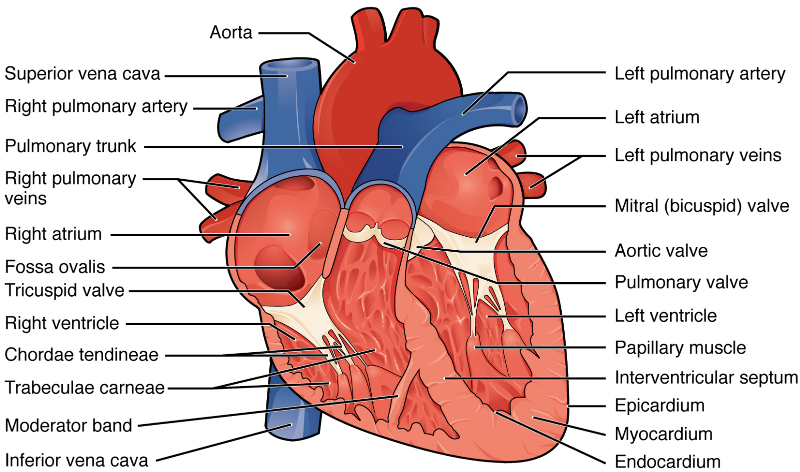
Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum**. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a **valve**, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular valves**. The valves at the openings

that lead to the pulmonary trunk and aorta are known generically as **semilunar valves**. The interventricular septum is visible in [link]. In this figure, the atrioventricular septum has been removed to better show the bicupid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton**, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Internal Structures of the Heart

This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.



Anterior view

Disorders of the…

Heart: Heart Defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for “open.” It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign, asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed

by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds. Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional

fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E2, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure.

Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term “tetralogy” is derived from the four components of the condition,

although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

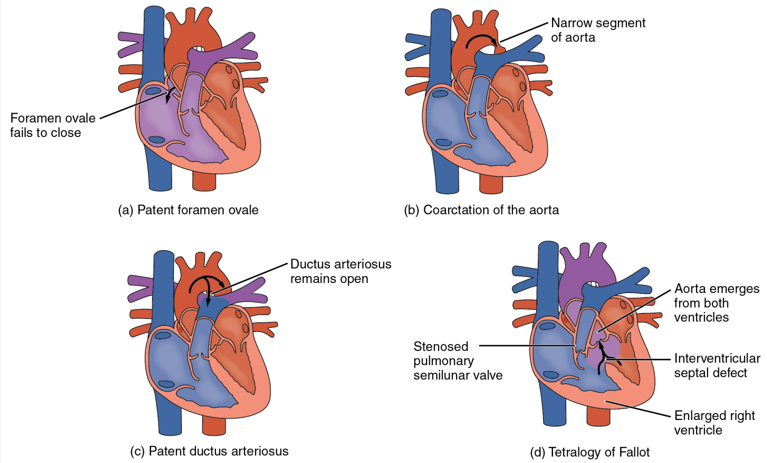
In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a “blue baby.” Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and

closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in [link].

Congenital Heart Defects

(a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.



Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic

circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the posterior portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in [link].

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

The atria receive venous blood on a nearly continuous basis, preventing venous flow from

stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

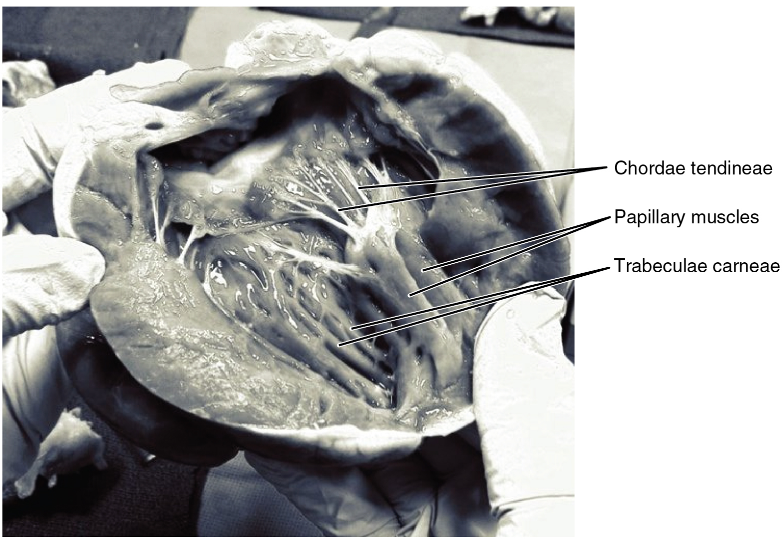
The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally "tendinous cords," or sometimes more poetically referred to as "heart strings." There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any

potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. [link] shows papillary muscles and chordae tendineae attached to the tricuspid valve.

Chordae Tendineae and Papillary Muscles

In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by “PV KS”/flickr.com)



The walls of the ventricle are lined with **trabeculae carneae**, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the **moderator band** (see

[link]) reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This

atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right (see [link]). Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

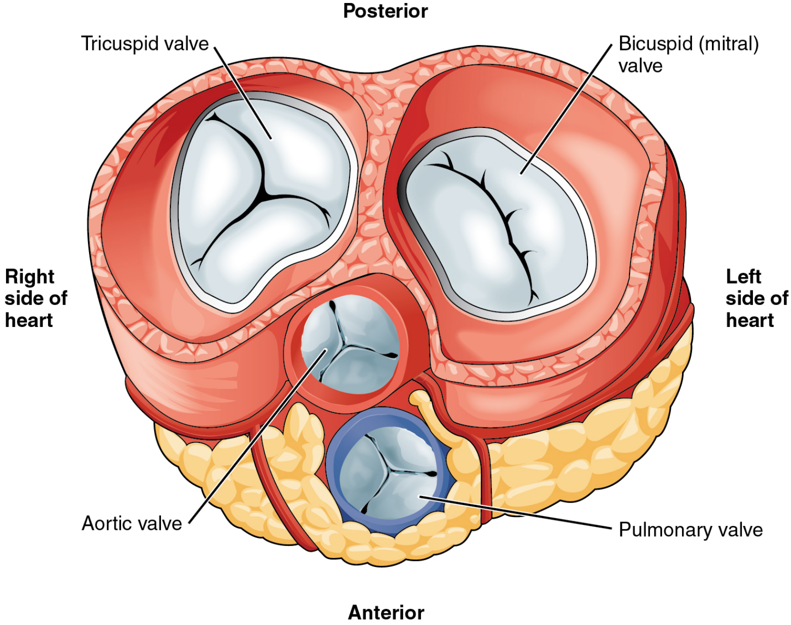
Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane ([link]). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced

with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.

Heart Valves

With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.



Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the **pulmonary valve**; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential

causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

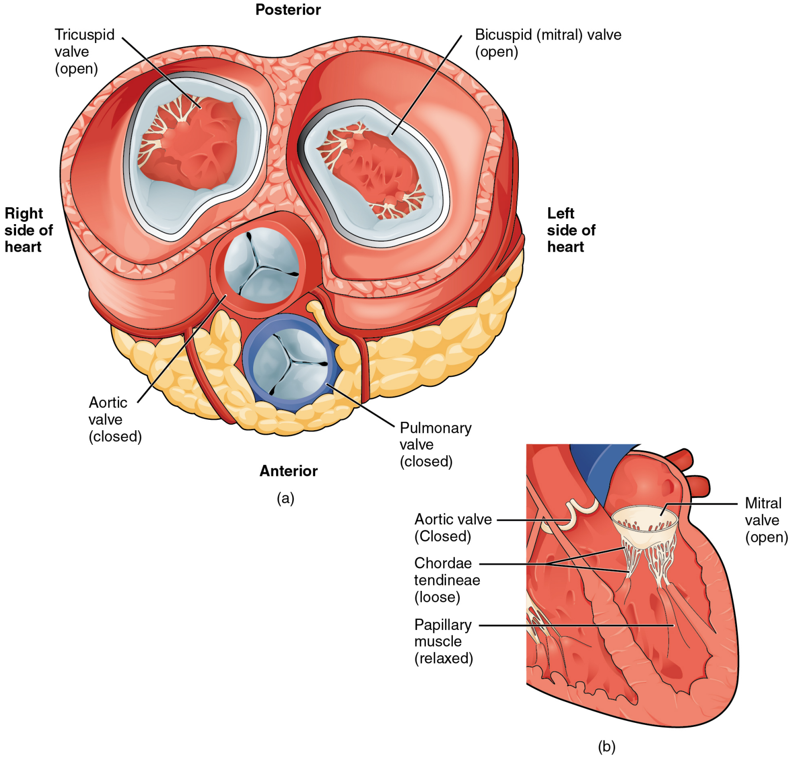
At the base of the aorta is the aortic semilunar valve, or the **aortic valve**, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In [link]**a**, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and

when the atria contract to pump blood into the ventricles. [link]**b** shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

Blood Flow from the Left Atrium to the Left Ventricle

(a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

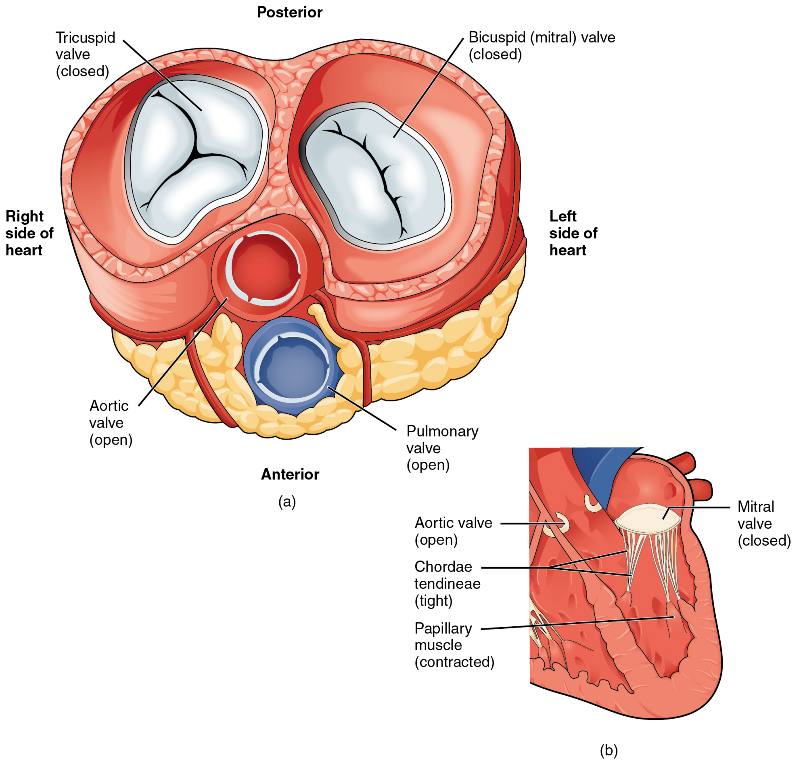


[link]**a** shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves prevents blood from being forced back into the atria. This stage can be seen from a frontal view in [link]**b**.

Blood Flow from the Left Ventricle into the Great Vessels

(a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels

have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.



When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed

and the tension on the chordae tendineae is slight (see [link]**b**). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see [link]**b**), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Visit this site to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been “removed” from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the

atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Disorders of the…

Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow

of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient’s condition will deteriorate dramatically and rapidly, and immediate surgical intervention may be required.

Auscultation, or listening to a patient’s heart

sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for “to listen,” and the technique has been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an “echo,” may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Visit this site for a free download, including excellent animations and audio of heart sounds.

Career Connection

Cardiologist

Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.

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Visit this site to learn more about cardiologists.

Career Connection

Cardiovascular Technologist/Technician

Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of $49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.

There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered

Phlebology Sonographer (RPhS).

Visit this site for more information on cardiovascular technologists/technicians.

Coronary Circulation

You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not

continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

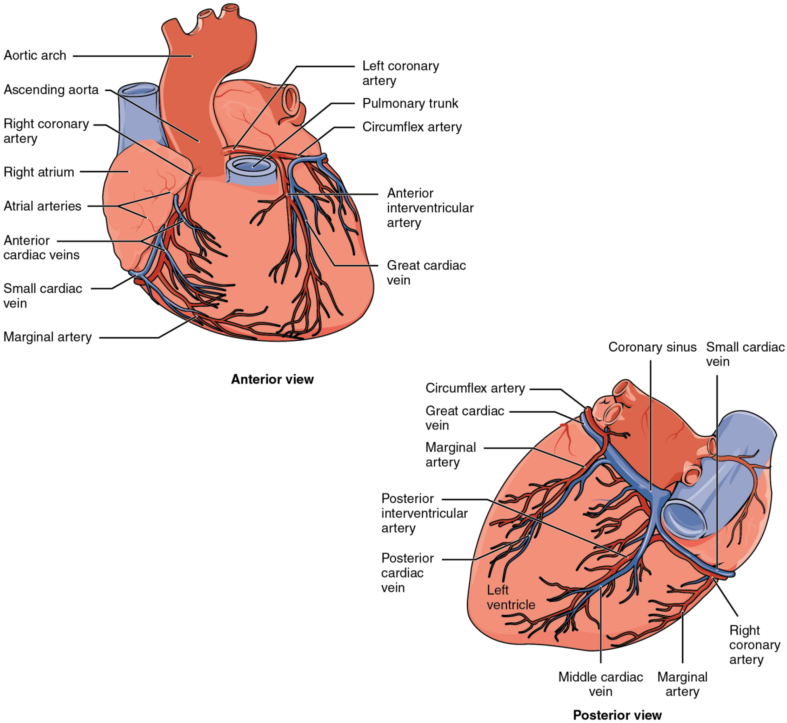
The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger **anterior interventricular artery**, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk.

Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An **anastomosis** is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in death of the cells (myocardial infarction) supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more marginal arteries arise from the right coronary artery inferior to the right atrium. The **marginal arteries** supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the **posterior interventricular artery**, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles. [link] presents views of the coronary circulation from both the anterior and posterior views.

Coronary Circulation

The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.



Diseases of the…

Heart: Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque

consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel.

In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient’s

ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells.

Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement

with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future. MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as "bad" cholesterol), low levels of high-density lipoprotein (HDL, or "good" cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries (see [link]). The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the anterior interventricular artery and drains the areas supplied by this vessel. It receives several major

branches, including the posterior cardiac vein, the middle cardiac vein, and the small cardiac vein. The **posterior cardiac vein** parallels and drains the areas supplied by the marginal artery branch of the circumflex artery. The **middle cardiac vein** parallels and drains the areas supplied by the posterior interventricular artery. The **small cardiac vein** parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

Diseases of the…

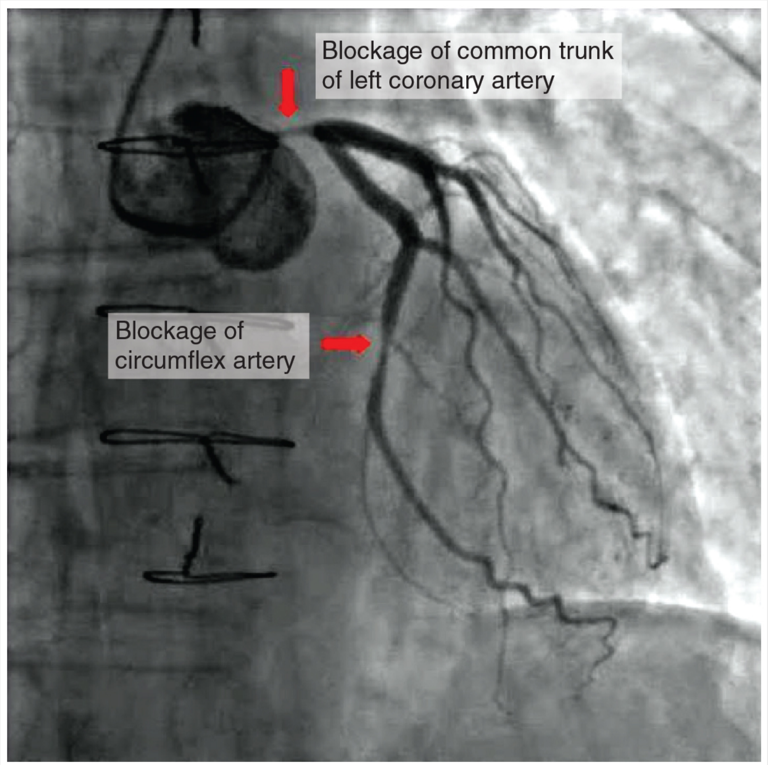
Heart: Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of

the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. [link] shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.

Atherosclerotic Coronary Arteries

In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).



The disease progresses slowly and often begins in children and can be seen as fatty “streaks” in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is

inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Chapter Review

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the atrioventricular septum. Two of these openings are guarded by the atrioventricular valves, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base

of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

Interactive Link Questions

Visit this site to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

The pressure gradient between the atria and the ventricles is much greater than that between the ventricles and the pulmonary trunk and aorta. Without the presence of the chordae tendineae and papillary muscles, the valves would be blown back (prolapsed) into the atria and blood would regurgitate.

Review Questions

Which of the following is not important in preventing backflow of blood?

1. chordae tendineae
2. papillary muscles
3. AV valves
4. endocardium

D

Which valve separates the left atrium from the left ventricle?

1. mitral
2. tricuspid
3. pulmonary
4. aortic

A

Which of the following lists the valves in the order through which the blood flows from the vena cava through the heart?

1. tricuspid, pulmonary semilunar, bicuspid,

aortic semilunar
2. mitral, pulmonary semilunar, bicuspid, aortic semilunar
3. aortic semilunar, pulmonary semilunar, tricuspid, bicuspid
4. bicuspid, aortic semilunar, tricuspid, pulmonary semilunar

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A

Which chamber initially receives blood from the systemic circuit?

1. left atrium
2. left ventricle
3. right atrium
4. right ventricle

C

The _____ layer secretes chemicals that help to regulate ionic environments and strength of contraction and serve as powerful vasoconstrictors.

1. pericardial sac
2. endocardium
3. myocardium

4. epicardium

B

The myocardium would be the thickest in the ______.

1. left atrium
2. left ventricle
3. right atrium
4. right ventricle

B

In which septum is it normal to find openings in the adult?

1. interatrial septum
2. interventricular septum
3. atrioventricular septum
4. all of the above

C

Critical Thinking Questions

Describe how the valves keep the blood moving in one direction.

When the ventricles contract and pressure begins to rise in the ventricles, there is an initial tendency for blood to flow back (regurgitate) to the atria. However, the papillary muscles also contract, placing tension on the chordae tendineae and holding the atrioventricular valves (tricuspid and mitral) in place to prevent the valves from prolapsing and being forced back into the atria. The semilunar valves (pulmonary and aortic) lack chordae tendineae and papillary muscles, but do not face the same pressure gradients as do the atrioventricular valves. As the ventricles relax and pressure drops within the ventricles, there is a tendency for the blood to flow backward. However, the valves, consisting of reinforced endothelium and connective tissue, fill with blood and seal off the opening preventing the return of blood.

Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

The pulmonary circuit consists of blood flowing to and from the lungs, whereas the systemic circuit carries blood to and from the entire body. The systemic circuit is far more extensive, consisting of far more vessels and offers much greater resistance to the flow of blood, so the heart must generate a higher pressure to overcome this resistance. This can be seen in the thickness of the myocardium in the ventricles.

Glossary

anastomosis
: (plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

anterior cardiac veins
: vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

anterior interventricular artery
: (also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

anterior interventricular sulcus
: sulcus located between the left and right

ventricles on the anterior surface of the heart

aortic valve
: (also, aortic semilunar valve) valve located at the base of the aorta

atrioventricular septum
: cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular valves
: one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium
: (plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

auricle
: extension of an atrium visible on the superior surface of the heart

bicuspid valve
: (also, mitral valve or left atrioventricular

valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

cardiac notch
: depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

cardiac skeleton
: (also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiomyocyte
: muscle cell of the heart

chordae tendineae
: string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

circumflex artery
: branch of the left coronary artery that follows coronary sulcus

coronary arteries
: branches of the ascending aorta that supply

blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus
: large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus
: sulcus that marks the boundary between the atria and ventricles

coronary veins
: vessels that drain the heart and generally parallel the large surface arteries

endocardium
: innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endothelium
: layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

epicardial coronary arteries
: surface arteries of the heart that generally follow the sulci

epicardium
: innermost layer of the serous pericardium and the outermost layer of the heart wall

foramen ovale
: opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

fossa ovalis
: oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

great cardiac vein
: vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

hypertrophic cardiomyopathy
: pathological enlargement of the heart, generally for no known reason

inferior vena cava
: large systemic vein that returns blood to the

heart from the inferior portion of the body

interatrial septum
: cardiac septum located between the two atria; contains the fossa ovalis after birth

interventricular septum
: cardiac septum located between the two ventricles

left atrioventricular valve
: (also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

marginal arteries
: branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

mesothelium
: simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium)

middle cardiac vein
: vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

mitral valve
: (also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

moderator band
: band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart

myocardium
: thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

papillary muscle
: extension of the myocardium in the ventricles to which the chordae tendineae attach

pectinate muscles
: muscular ridges seen on the anterior surface of the right atrium

pericardial cavity
: cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

pericardial sac
(also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pericardium
(also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

posterior cardiac vein
vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein

posterior interventricular artery
(also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles

posterior interventricular sulcus
sulcus located between the left and right ventricles on the anterior surface of the heart

pulmonary arteries
: left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary capillaries
: capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit
: blood flow to and from the lungs

pulmonary trunk
: large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary valve
: (also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary veins
: veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

right atrioventricular valve
: (also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

semilunar valves
: valves located at the base of the pulmonary trunk and at the base of the aorta

septum
: (plural = septa) walls or partitions that divide the heart into chambers

septum primum
: flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

small cardiac vein
: parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

sulcus
: (plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superior vena cava
: large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit
: blood flow to and from virtually all of the tissues of the body

trabeculae carneae
: ridges of muscle covered by endocardium located in the ventricles

tricuspid valve
: term used most often in clinical settings for the right atrioventricular valve

valve
: in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

ventricle
: one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

Cardiac Cycle

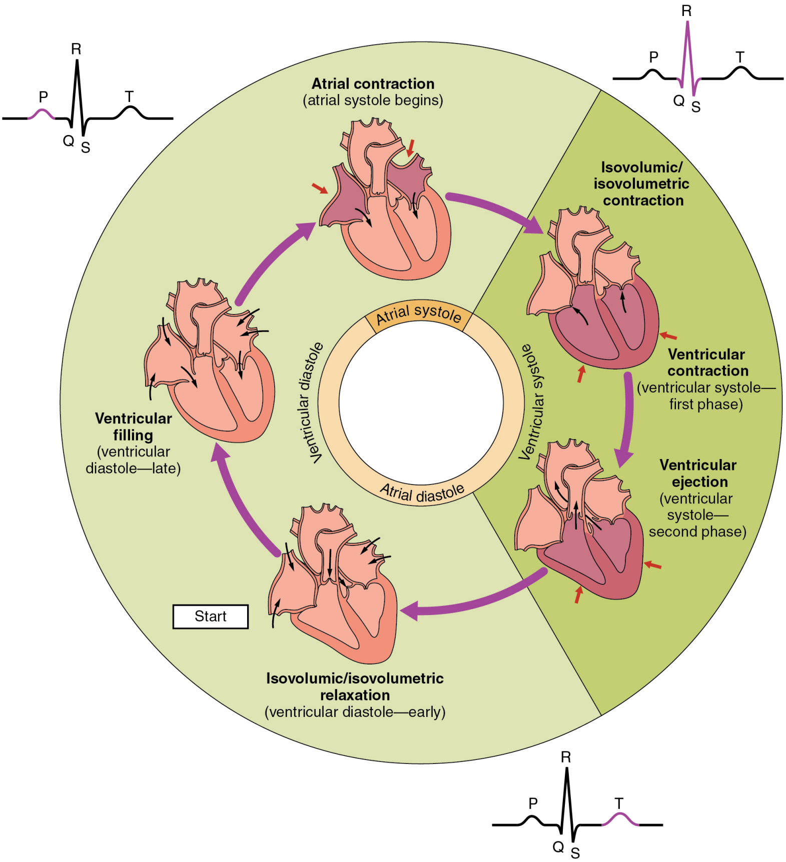
By the end of this section, you will be able to:

- Describe the relationship between blood pressure and blood flow
- Summarize the events of the cardiac cycle
- Compare atrial and ventricular systole and diastole
- Relate heart sounds detected by auscultation to action of heart's valves

The period of time that begins with contraction of the atria and ends with ventricular relaxation is known as the **cardiac cycle** ([link]). The period of contraction that the heart undergoes while it pumps blood into circulation is called **systole**. The period of relaxation that occurs as the chambers fill with blood is called **diastole**. Both the atria and ventricles undergo systole and diastole, and it is essential that these components be carefully regulated and coordinated to ensure blood is pumped efficiently to the body.

Overview of the Cardiac Cycle

The cardiac cycle begins with atrial systole and progresses to ventricular systole, atrial diastole, and ventricular diastole, when the cycle begins again. Correlations to the ECG are highlighted.



Pressures and Flow

Fluids, whether gases or liquids, are materials that flow according to pressure gradients—that is, they move from regions that are higher in pressure to regions that are lower in pressure. Accordingly, when the heart chambers are relaxed (diastole), blood will flow into the atria from the veins, which are higher in pressure. As blood flows into the atria,

the pressure will rise, so the blood will initially move passively from the atria into the ventricles. When the action potential triggers the muscles in the atria to contract (atrial systole), the pressure within the atria rises further, pumping blood into the ventricles. During ventricular systole, pressure rises in the ventricles, pumping blood into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle. Again, as you consider this flow and relate it to the conduction pathway, the elegance of the system should become apparent.

Phases of the Cardiac Cycle

At the beginning of the cardiac cycle, both the atria and ventricles are relaxed (diastole). Blood is flowing into the right atrium from the superior and inferior venae cavae and the coronary sinus. Blood flows into the left atrium from the four pulmonary veins. The two atrioventricular valves, the tricuspid and mitral valves, are both open, so blood flows unimpeded from the atria and into the ventricles. Approximately 70–80 percent of ventricular filling occurs by this method. The two semilunar valves, the pulmonary and aortic valves, are closed, preventing backflow of blood into the right and left ventricles from the pulmonary trunk on the right and the aorta on the left.

Atrial Systole and Diastole

Contraction of the atria follows depolarization, represented by the P wave of the ECG. As the atrial muscles contract from the superior portion of the atria toward the atrioventricular septum, pressure rises within the atria and blood is pumped into the ventricles through the open atrioventricular (tricuspid, and mitral or bicuspid) valves. At the start of atrial systole, the ventricles are normally filled with approximately 70–80 percent of their capacity due to inflow during diastole. Atrial contraction, also referred to as the “atrial kick,” contributes the remaining 20–30 percent of filling (see [link]). Atrial systole lasts approximately 100 ms and ends prior to ventricular systole, as the atrial muscle returns to diastole.

Ventricular Systole

Ventricular systole (see [link]) follows the depolarization of the ventricles and is represented by the QRS complex in the ECG. It may be conveniently divided into two phases, lasting a total of 270 ms. At the end of atrial systole and just prior to atrial contraction, the ventricles contain approximately 130 mL blood in a resting adult in a standing position. This volume is known as the **end diastolic volume (EDV)** or **preload**.

Initially, as the muscles in the ventricle contract, the

pressure of the blood within the chamber rises, but it is not yet high enough to open the semilunar (pulmonary and aortic) valves and be ejected from the heart. However, blood pressure quickly rises above that of the atria that are now relaxed and in diastole. This increase in pressure causes blood to flow back toward the atria, closing the tricuspid and mitral valves. Since blood is not being ejected from the ventricles at this early stage, the volume of blood within the chamber remains constant. Consequently, this initial phase of ventricular systole is known as **isovolumic contraction**, also called isovolumetric contraction (see [link]).

In the second phase of ventricular systole, the **ventricular ejection phase**, the contraction of the ventricular muscle has raised the pressure within the ventricle to the point that it is greater than the pressures in the pulmonary trunk and the aorta. Blood is pumped from the heart, pushing open the pulmonary and aortic semilunar valves. Pressure generated by the left ventricle will be appreciably greater than the pressure generated by the right ventricle, since the existing pressure in the aorta will be so much higher. Nevertheless, both ventricles pump the same amount of blood. This quantity is referred to as stroke volume. Stroke volume will normally be in the range of 70–80 mL. Since ventricular systole began with an EDV of approximately 130 mL of blood, this means that there is still 50–60 mL of blood remaining in the

ventricle following contraction. This volume of blood is known as the **end systolic volume (ESV)**.

Ventricular Diastole

Ventricular relaxation, or diastole, follows repolarization of the ventricles and is represented by the T wave of the ECG. It too is divided into two distinct phases and lasts approximately 430 ms.

During the early phase of ventricular diastole, as the ventricular muscle relaxes, pressure on the remaining blood within the ventricle begins to fall. When pressure within the ventricles drops below pressure in both the pulmonary trunk and aorta, blood flows back toward the heart, producing the dicrotic notch (small dip) seen in blood pressure tracings. The semilunar valves close to prevent backflow into the heart. Since the atrioventricular valves remain closed at this point, there is no change in the volume of blood in the ventricle, so the early phase of ventricular diastole is called the **isovolumic ventricular relaxation phase**, also called isovolumetric ventricular relaxation phase (see [link]).

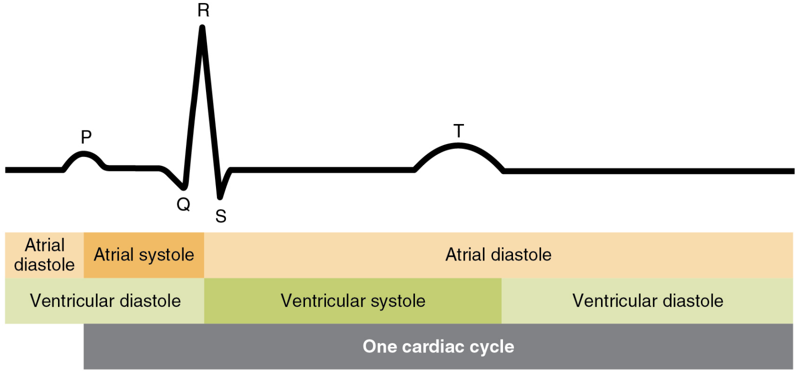
In the second phase of ventricular diastole, called late ventricular diastole, as the ventricular muscle relaxes, pressure on the blood within the ventricles drops even further. Eventually, it drops below the pressure in the atria. When this occurs, blood flows

from the atria into the ventricles, pushing open the tricuspid and mitral valves. As pressure drops within the ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles. Both chambers are in diastole, the atrioventricular valves are open, and the semilunar valves remain closed (see [link]). The cardiac cycle is complete.

[link] illustrates the relationship between the cardiac cycle and the ECG.

Relationship between the Cardiac Cycle and ECG

Initially, both the atria and ventricles are relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contraction (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS complex represents depolarization of the ventricles and is followed by ventricular contraction. The T wave represents the repolarization of the ventricles and marks the beginning of ventricular relaxation.



Heart Sounds

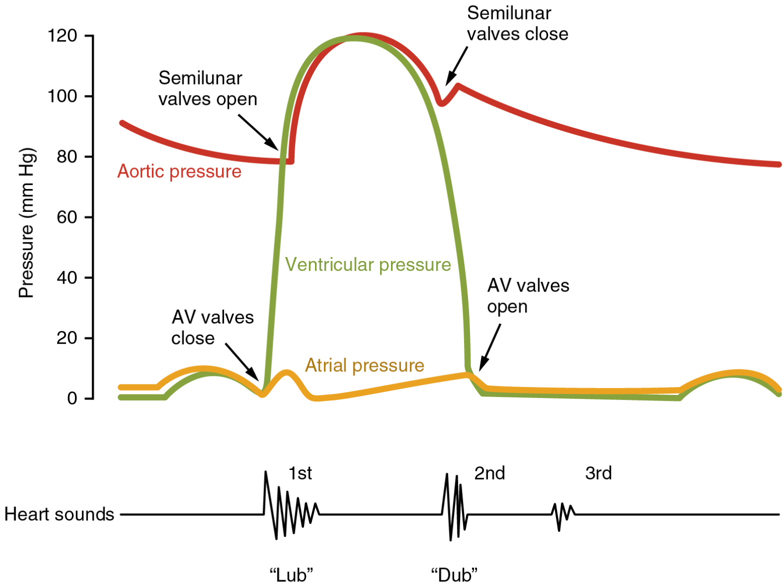
One of the simplest, yet effective, diagnostic techniques applied to assess the state of a patient's heart is auscultation using a stethoscope.

In a normal, healthy heart, there are only two audible **heart sounds**: S1 and S2. S1 is the sound created by the closing of the atrioventricular valves during ventricular contraction and is normally described as a "lub," or first heart sound. The second heart sound, S2, is the sound of the closing of the semilunar valves during ventricular diastole and is described as a "dub" ([link]). In both cases, as the valves close, the openings within the atrioventricular septum guarded by the valves will become reduced, and blood flow through the opening will become more turbulent until the valves are fully closed. There is a third heart sound, S3, but it is rarely heard in healthy individuals. It may be the sound of blood flowing into the atria, or blood sloshing back and forth in the ventricle, or even tensing of the chordae tendineae. S3 may be heard in youth, some athletes, and pregnant women. If the sound is heard later in life, it may indicate congestive heart failure, warranting further tests. Some cardiologists refer to the collective S1, S2, and S3 sounds as the "Kentucky gallop," because they mimic those produced by a galloping horse. The fourth heart sound, S4, results from the contraction of the atria pushing blood into a stiff or

hypertrophic ventricle, indicating failure of the left ventricle. S4 occurs prior to S1 and the collective sounds S4, S1, and S2 are referred to by some cardiologists as the "Tennessee gallop," because of their similarity to the sound produced by a galloping horse with a different gait. A few individuals may have both S3 and S4, and this combined sound is referred to as S7.

Heart Sounds and the Cardiac Cycle

In this illustration, the x-axis reflects time with a recording of the heart sounds. The y-axis represents pressure.



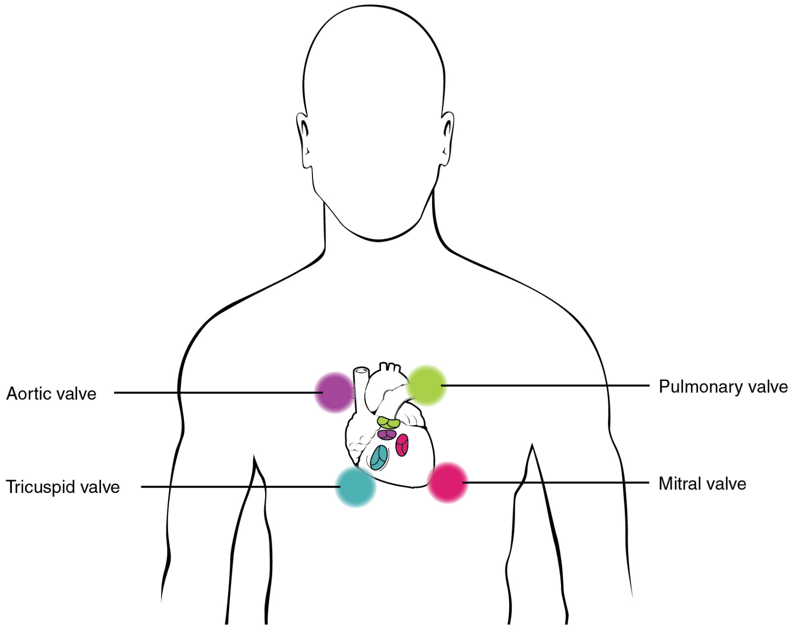
The term **murmur** is used to describe an unusual sound coming from the heart that is caused by the turbulent flow of blood. Murmurs are graded on a scale of 1 to 6, with 1 being the most common, the most difficult sound to detect, and the least serious.

The most severe is a 6. Phonocardiograms or auscultograms can be used to record both normal and abnormal sounds using specialized electronic stethoscopes.

During auscultation, it is common practice for the clinician to ask the patient to breathe deeply. This procedure not only allows for listening to airflow, but it may also amplify heart murmurs. Inhalation increases blood flow into the right side of the heart and may increase the amplitude of right-sided heart murmurs. Expiration partially restricts blood flow into the left side of the heart and may amplify left-sided heart murmurs. [link] indicates proper placement of the bell of the stethoscope to facilitate auscultation.

Stethoscope Placement for Auscultation

Proper placement of the bell of the stethoscope facilitates auscultation. At each of the four locations on the chest, a different valve can be heard.



Chapter Review

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract (atrial systole), following depolarization of the atria, and pump blood into the ventricles. The ventricles begin to contract (ventricular systole), raising pressure within the ventricles. When ventricular pressure rises above the pressure in the atria, blood flows toward the atria, producing the

first heart sound, S1 or lub. As pressure in the ventricles rises above two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax (ventricular diastole), and pressure within the ventricles drops. As ventricular pressure drops, there is a tendency for blood to flow back into the atria from the major arteries, producing the dicrotic notch in the ECG and closing the two semilunar valves. The second heart sound, S2 or dub, occurs when the semilunar valves close. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle. The valves prevent backflow of blood. Failure of the valves to operate properly produces turbulent blood flow within the heart; the resulting heart murmur can often be heard with a stethoscope.

Review Questions

The cardiac cycle consists of a distinct relaxation and contraction phase. Which term is typically used to refer ventricular contraction while no blood is being ejected?

1. systole
2. diastole
3. quiescent
4. isovolumic contraction

D

Most blood enters the ventricle during _____.

1. atrial systole
2. atrial diastole
3. ventricular systole
4. isovolumic contraction

B

The first heart sound represents which portion of the cardiac cycle?

1. atrial systole
2. ventricular systole
3. closing of the atrioventricular valves
4. closing of the semilunar valves

C

Ventricular relaxation immediately follows ______.

1. atrial depolarization
2. ventricular repolarization
3. ventricular depolarization
4. atrial repolarization

B

Critical Thinking Questions

Describe one cardiac cycle, beginning with both atria and ventricles relaxed.

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract following depolarization of the atria and pump blood into the ventricles. The ventricles begin to contract, raising pressure within the ventricles. When ventricular pressure rises above the pressure in

the two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax, and pressure within the ventricles drops. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle.

Glossary

cardiac cycle
: period of time between the onset of atrial contraction (atrial systole) and ventricular relaxation (ventricular diastole)

diastole
: period of time when the heart muscle is relaxed and the chambers fill with blood

end diastolic volume (EDV)
: (also, preload) the amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

end systolic volume (ESV)
: amount of blood remaining in each ventricle following systole

heart sounds
: sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves (“lub”) and semilunar valves (“dub”)

isovolumic contraction
: (also, isovolumetric contraction) initial phase of ventricular contraction in which tension and pressure in the ventricle increase, but no blood is pumped or ejected from the heart

isovolumic ventricular relaxation phase
: initial phase of the ventricular diastole when pressure in the ventricles drops below pressure in the two major arteries, the pulmonary trunk, and the aorta, and blood attempts to flow back into the ventricles, producing the dicrotic notch of the ECG and closing the two semilunar valves

murmur
: unusual heart sound detected by auscultation; typically related to septal or valve defects

preload
: (also, end diastolic volume) amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

systole
: period of time when the heart muscle is

contracting

ventricular ejection phase
: second phase of ventricular systole during which blood is pumped from the ventricle

Introduction
class="introduction"
Blood Vessels
While most blood vessels are located deep from the surface and are not visible, the superficial veins of the upper limb provide an indication of the extent, prominence, and importance of these structures to the body. (credit: Colin Davis)

Chapter Objectives

After studying this chapter, you will be able to:

- Compare and contrast the anatomical structure of arteries, arterioles, capillaries, venules, and veins
- Accurately describe the forces that account for capillary exchange

- List the major factors affecting blood flow, blood pressure, and resistance
- Describe how blood flow, blood pressure, and resistance interrelate
- Discuss how the neural and endocrine mechanisms maintain homeostasis within the blood vessels
- Describe the interaction of the cardiovascular system with other body systems
- Label the major blood vessels of the pulmonary and systemic circulations
- Identify and describe the hepatic portal system
- Describe the development of blood vessels and fetal circulation
- Compare fetal circulation to that of an individual after birth

In this chapter, you will learn about the vascular part of the cardiovascular system, that is, the vessels that transport blood throughout the body and provide the physical site where gases, nutrients, and other substances are exchanged with body cells. When vessel functioning is reduced, blood-borne substances do not circulate effectively throughout the body. As a result, tissue injury occurs, metabolism is impaired, and the functions of every bodily system are threatened.

Structure and Function of Blood Vessels

By the end of this section, you will be able to:

- Compare and contrast the three tunics that make up the walls of most blood vessels
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function
- Describe the basic structure of a capillary bed, from the supplying metarteriole to the venule into which it drains
- Explain the structure and function of venous valves in the large veins of the extremities

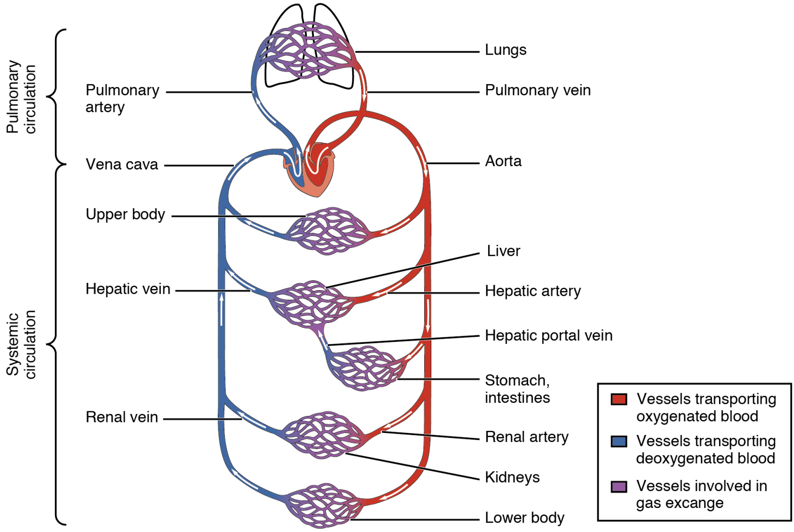
Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit ([link]). Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has

been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

Cardiovascular Circulation

The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

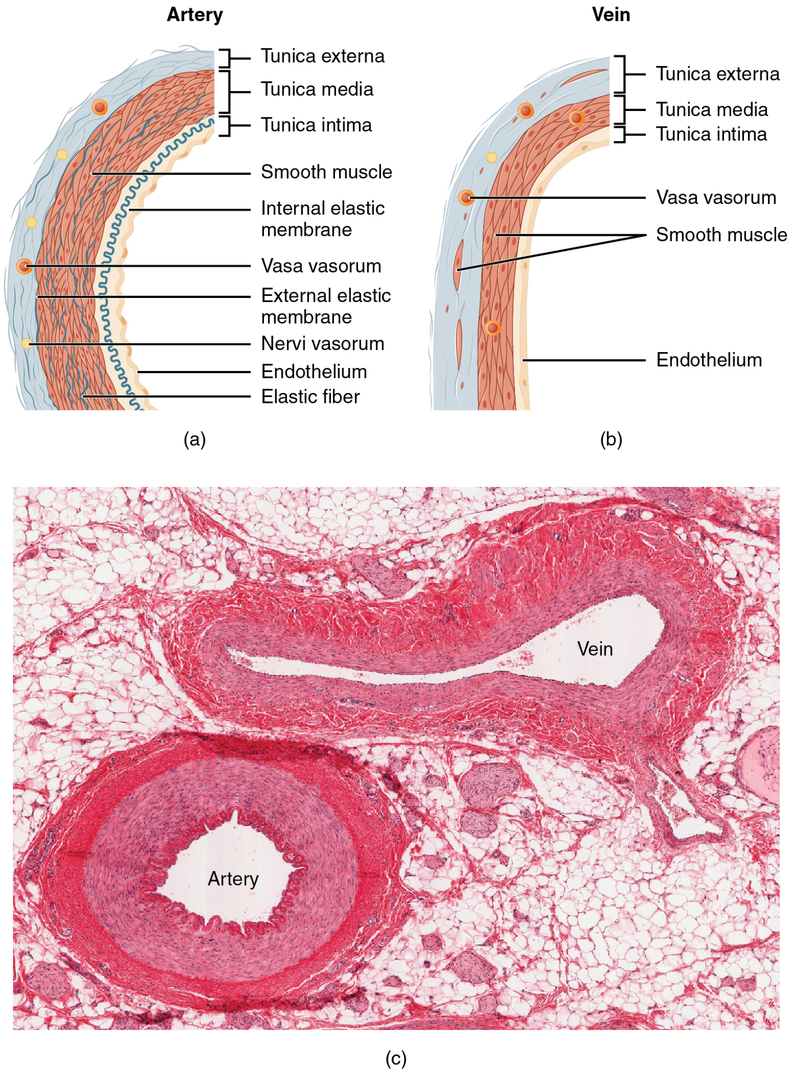


Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure ([link]). Each type of vessel has a **lumen**—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

Structure of Blood Vessels

(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)



By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are

considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel's cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the **vasa vasorum**—literally "vessels of the vessel"—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel (see [link]) or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the

outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa (see [link]). [link] compares and contrasts the tunics of the arteries and veins.

Comparison of Tunics in Arteries and Veins

	Arteries	Veins
General appearance	Thick walls with small lumens Generally appear	Thin walls with large lumens Generally appear

	rounded	flattened
Tunica intima	Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels	Endothelium appears smooth Internal elastic membrane absent
Tunica media	Normally the thickest layer in arteries Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart) External elastic membrane present in larger vessels	Normally thinner than the tunica externa Smooth muscle cells and collagenous fibers predominate Nervi vasorum and vasa vasorum present External elastic membrane absent
Tunica externa	Normally thinner than the tunica media in all but the largest arteries Collagenous and	Normally the thickest layer in veins Collagenous and smooth fibers predominate

	elastic fibers Nervi vasorum and vasa vasorum present	Some smooth muscle fibers Nervi vasorum and vasa vasorum present

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane,

or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the **internal elastic membrane** (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood

vessel walls.

Tunica Media

The **tunica media** is the substantial middle layer of the vessel wall (see [link]). It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, **vasoconstriction** decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as **nervi vasorum**, or “nerves of the vessel,” that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Parasympathetic stimulation does trigger

vasodilation as well as erection during sexual arousal in the external genitalia of both sexes. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the **external elastic membrane** (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

The outer tunic, the **tunica externa** (also called the

tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

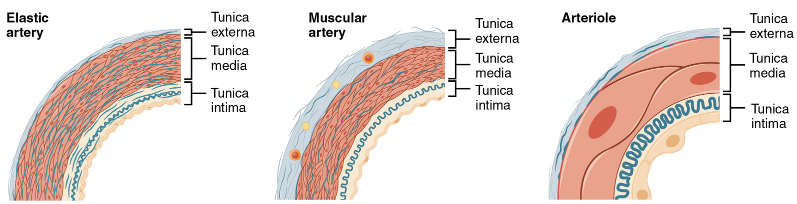
Arteries

An **artery** is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an **elastic artery** ([link]). Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to

recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Types of Arteries and Arterioles

Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.



Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery’s tunica intima decreases and the amount of smooth muscle in its tunica media increases. The

artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see [link]).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A **capillary** is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through.

Flow through capillaries is often described as **microcirculation**.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of "leakiness:" continuous, fenestrated, and sinusoid capillaries ([link]).

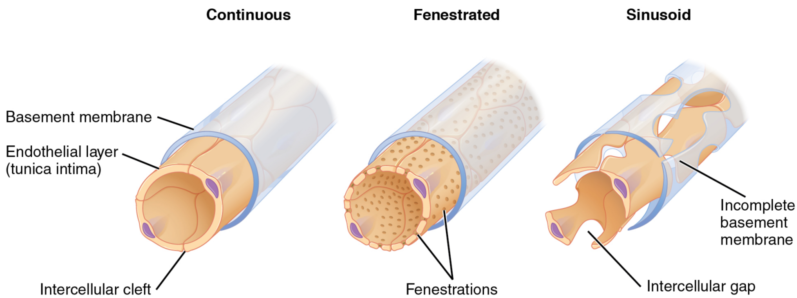
Continuous Capillaries

The most common type of capillary, the **continuous capillary**, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between

cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

Types of Capillaries

The three major types of capillaries: continuous, fenestrated, and sinusoid.



Fenestrated Capillaries

A **fenestrated capillary** is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location. Fenestrated capillaries are common in the small intestine, which

is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

A **sinusoid capillary** (or sinusoid) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires extensive specialized sinusoid capillaries in order to

process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

Metarterioles and Capillary Beds

A **metarteriole** is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once

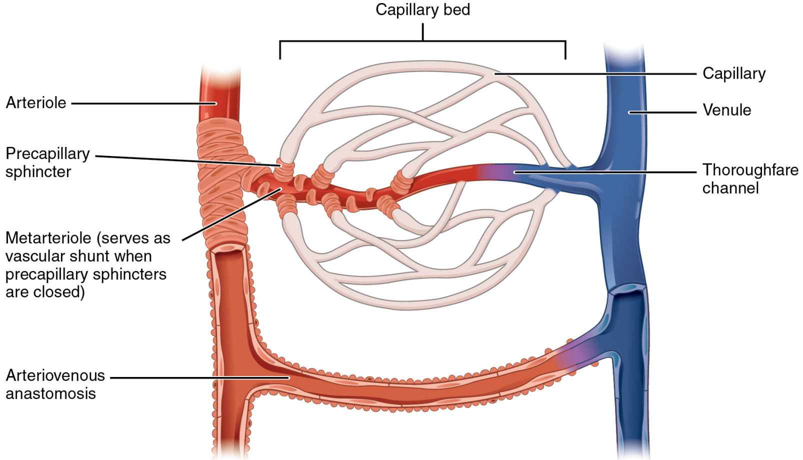
more ([link]). If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a **thoroughfare channel** and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a **vascular shunt**. In addition, an **arteriovenous anastomosis** may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called **vasomotion** and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

Capillary Bed

In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the

metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.



Venules

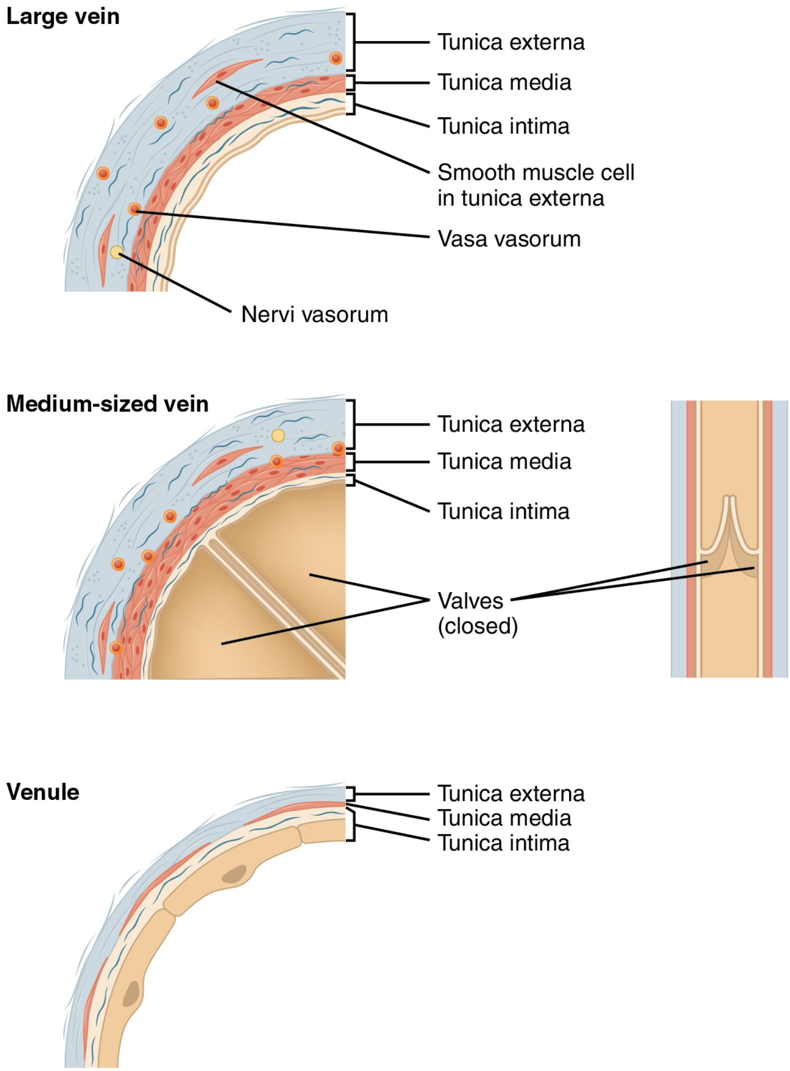
A **venule** is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa ([link]). Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

Veins

A **vein** is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens (see [link]). Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity. [link] compares the features of arteries and veins.

Comparison of Veins and Venules

Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.



Comparison of

Arteries and Veins		
	Arteries	**Veins**
Direction of blood flow	Conducts blood away from the heart	Conducts blood toward the heart
General appearance	Rounded	Irregular, often collapsed
Pressure	High	Low
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries Lower in pulmonary arteries	Lower in systemic veins Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

Disorders of the…

Cardiovascular System: Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of

gravity. Any blood that accumulates in a vein will increase the pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Varicose Veins

Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriese)

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs ([link]). This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are

often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time ([link]). Their ability to hold this much blood is due to their high **capacitance**, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they

are said to be **capacitance vessels**.

Distribution of Blood Flow

Systemic circulation 84%	Systemic veins 64%	Large veins 18%
		Large venous networks (liver, bone marrow, and integument) 21%
		Venules and medium-sized veins 25%
	Systemic arteries 13%	Arterioles 2%
		Muscular arteries 5%
		Elastic arteries 4%
		Aorta 2%
	Systemic capillaries 7%	Systemic capillaries 7%
Pulmonary circulation 9%	Pulmonary veins 4%	
	Pulmonary capillaries 2%	
	Pulmonary arteries 3%	
Heart 7%		

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a "stiffening" of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in [link],

approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction, this “reserve” volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

Career Connection

Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also

include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

Visit this site to learn more about vascular surgery.

Visit this site to learn more about vascular technicians.

Chapter Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the tunica intima, tunica media, and tunica externa. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as endothelium and a small

amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

Review Questions

The endothelium is found in the _____.

1. tunica intima
2. tunica media
3. tunica externa
4. lumen

A

Nervi vasorum control _____.

1. vasoconstriction
2. vasodilation
3. capillary permeability
4. both vasoconstriction and vasodilation

D

Closer to the heart, arteries would be expected to have a higher percentage of ______.

1. endothelium
2. smooth muscle fibers
3. elastic fibers
4. collagenous fibers

C

Which of the following best describes veins?

1. thick walled, small lumens, low pressure, lack valves
2. thin walled, large lumens, low pressure, have valves
3. thin walled, small lumens, high pressure, have valves
4. thick walled, large lumens, high pressure, lack valves

B

An especially leaky type of capillary found in the liver and certain other tissues is called a

_____.

1. capillary bed
2. fenestrated capillary
3. sinusoid capillary
4. metarteriole

C

Critical Thinking Questions

Arterioles are often referred to as resistance vessels. Why?

Arterioles receive blood from arteries, which are vessels with a much larger lumen. As their own lumen averages just 30 micrometers or less, arterioles are critical in slowing down—or resisting—blood flow. The arterioles can also constrict or dilate, which varies their resistance, to help distribute blood flow to the tissues.

Cocaine use causes vasoconstriction. Is this likely to increase or decrease blood pressure, and why?

Vasoconstriction causes the lumens of blood vessels to narrow. This increases the pressure of the blood flowing within the vessel.

A blood vessel with a few smooth muscle fibers and connective tissue, and only a very thin tunica externa conducts blood toward the heart. What type of vessel is this?

This is a venule.

Glossary

arteriole
: (also, resistance vessel) very small artery that leads to a capillary

arteriovenous anastomosis
: short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

artery
: blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

capacitance
: ability of a vein to distend and store blood

capacitance vessels
: veins

capillary
: smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed
: network of 10–100 capillaries connecting arterioles to venules

continuous capillary
: most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

elastic artery
: (also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

external elastic membrane
: membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

fenestrated capillary
: type of capillary with pores or fenestrations in the endothelium that allow for rapid passage

of certain small materials

internal elastic membrane
membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

lumen
interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

metarteriole
short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation
blood flow through the capillaries

muscular artery
(also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

nervi vasorum
small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

perfusion

distribution of blood into the capillaries so the tissues can be supplied

precapillary sphincters
: circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary

sinusoid capillary
: rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

thoroughfare channel
: continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

tunica externa
: (also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima
: (also, tunica interna) innermost lining or tunic of a vessel

tunica media
: middle layer or tunic of a vessel (except

capillaries)

vasa vasorum
: small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

vascular shunt
: continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vasoconstriction
: constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation
: relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vasomotion
: irregular, pulsating flow of blood through capillaries and related structures

vein
: blood vessel that conducts blood toward the heart

venous reserve
: volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

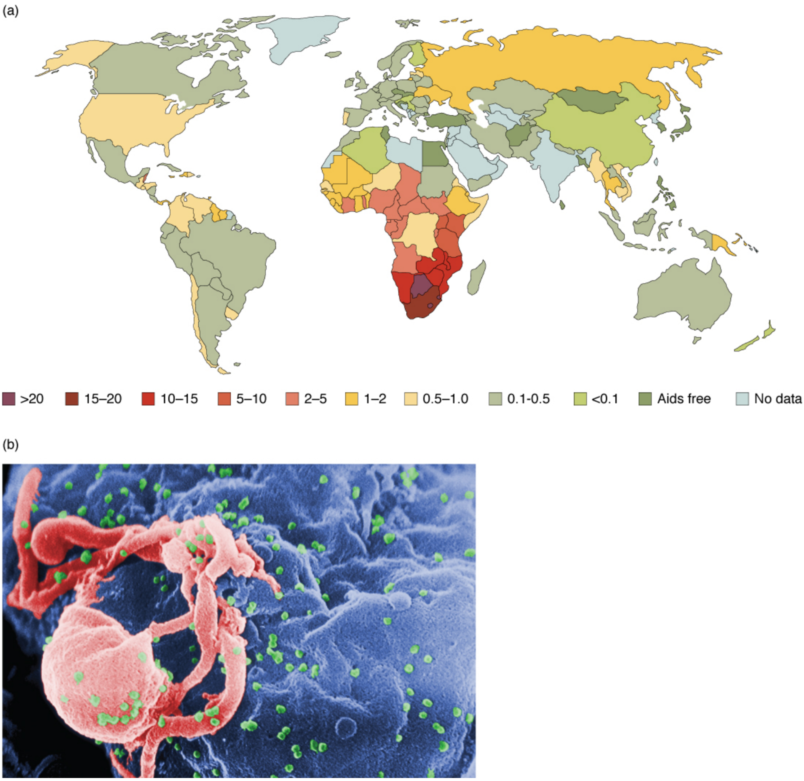
venule
: small vessel leading from the capillaries to veins

Introduction

class="introduction"

The Worldwide AIDS Epidemic

(a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries. This grim picture had changed little by 2012. (b) In this scanning electron micrograph, HIV virions (green particles) are budding off the surface of a macrophage (pink structure). (credit b: C. Goldsmith)



Chapter Objectives

After studying this chapter, you will be able to:

- Identify the components and anatomy of the lymphatic system
- Discuss the role of the innate immune response against pathogens
- Describe the power of the adaptive immune response to cure disease
- Explain immunological deficiencies and over-reactions of the immune system
- Discuss the role of the immune response in transplantation and cancer
- Describe the interaction of the immune and lymphatic systems with other body systems

In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune

systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi's sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstreams, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus (HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has transformed HIV infection into a chronic, manageable disease and not

the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public's attention became focused as never before on the importance of having a functional and healthy immune system.

Anatomy of the Lymphatic and Immune Systems
By the end of this section, you will be able to:

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain

body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes "backs up" from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

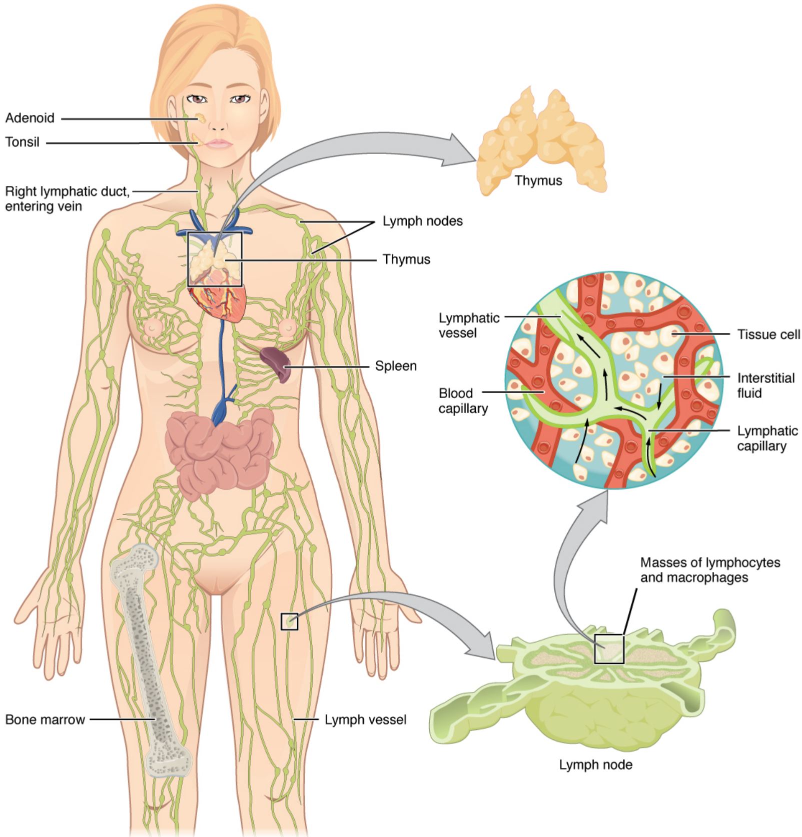
Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the

bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body ([link]).

Anatomy of the Lymphatic System

Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.



A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced

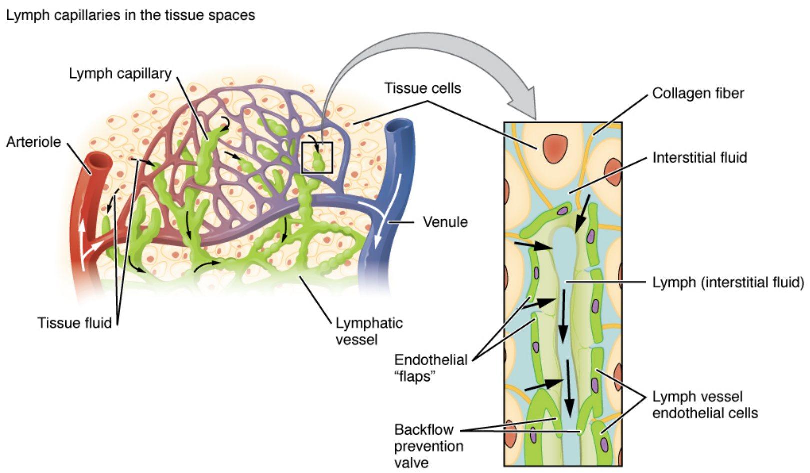
through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body ([link]). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

Lymphatic Capillaries

Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.



Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see [link]). When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then

travels through the lymphatic system, eventually entering the bloodstream.

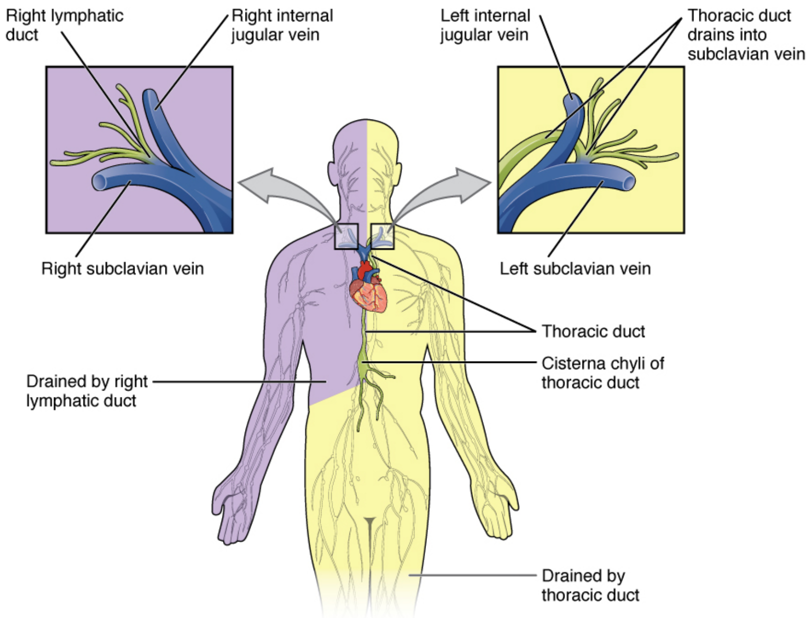
Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see [link]).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct ([link]). On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

Major Trunks and Ducts of the Lymphatic System

The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.



The overall drainage system of the body is asymmetrical (see [link]). The **right lymphatic duct** receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the **thoracic duct** via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells,

and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases based on the timing of their effects. The three temporal phases consist of the following:

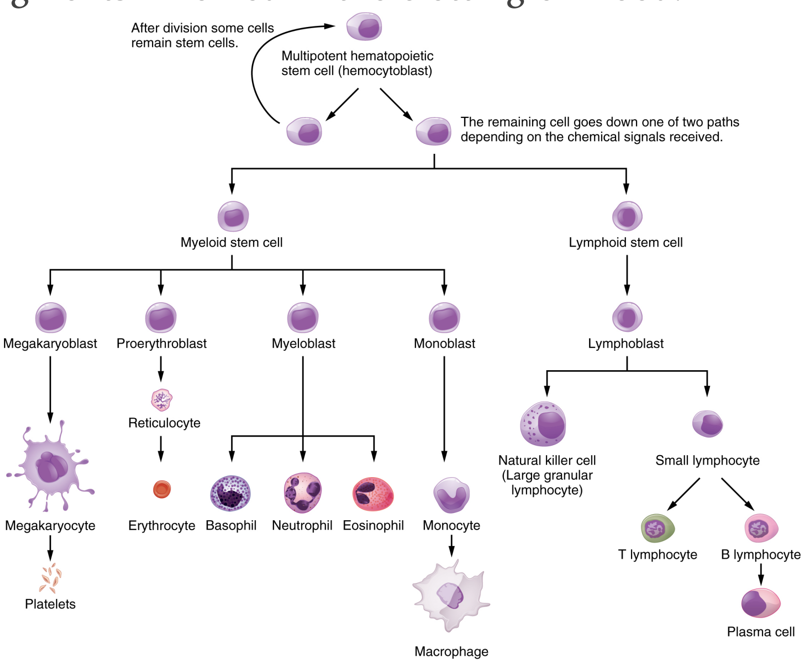
- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells ([link]). In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

Hematopoietic System of the Bone Marrow

All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.



Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses ([link]). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B

cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A **plasma cell** is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body’s first lines of defense against viruses and certain types of cancer.

Lymphocytes

Type of lymphocyte	**Primary function**
B lymphocyte	Generates diverse antibodies
T lymphocyte	Secretes chemical messengers
Plasma cell	Secretes antibodies
NK cell	Destroys virally infected cells

Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in an HIV infection?

Primary Lymphoid Organs and Lymphocyte Development

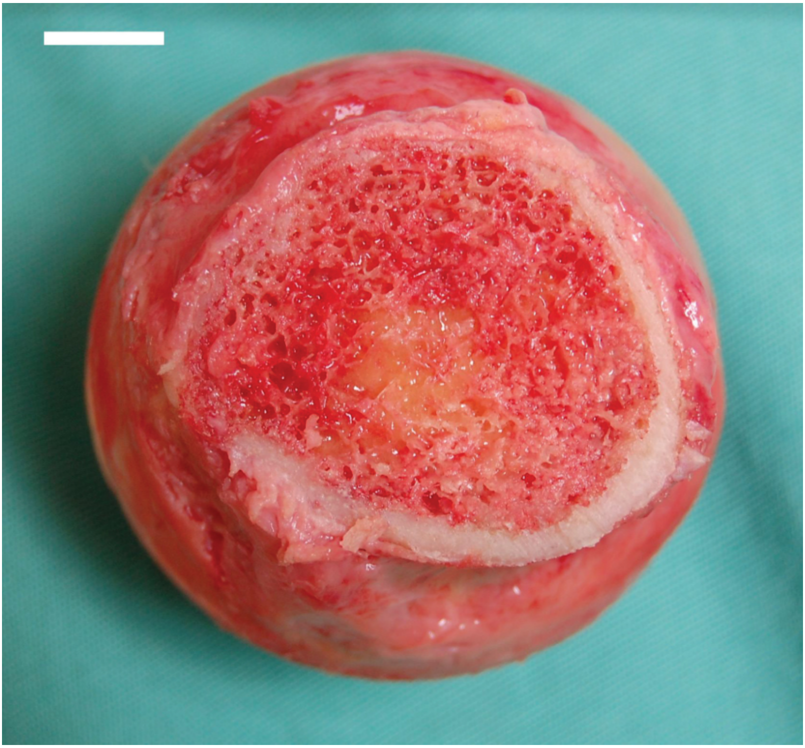
Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body's own cells relatively intact. The **primary lymphoid organs** are the bone marrow and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red **bone marrow** is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells ([link]). The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a **thymocyte**, leaves the bone marrow and matures largely in the thymus gland.

Bone Marrow

Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.



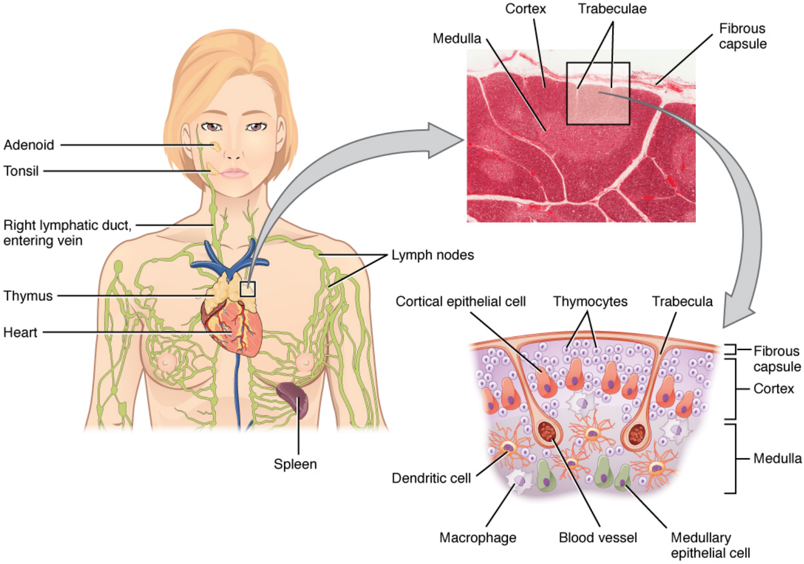
Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart ([link]). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

Location, Structure, and Histology of the Thymus

The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the

Regents of the University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail.

The connective tissue capsule further divides the

thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is densely packed so it stains more intensely than the rest of the thymus (see [link]). The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

Aging and the…

Immune System

By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one's life. At

that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.

Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXN1 gene with age.

It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases.

What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naïve T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will

likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the **secondary lymphoid organs**. A **naïve lymphocyte** is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- **Germinal centers**, which are the sites of

rapidly dividing and differentiating B lymphocytes
- Specialized post-capillary vessels known as **high endothelial venules**; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

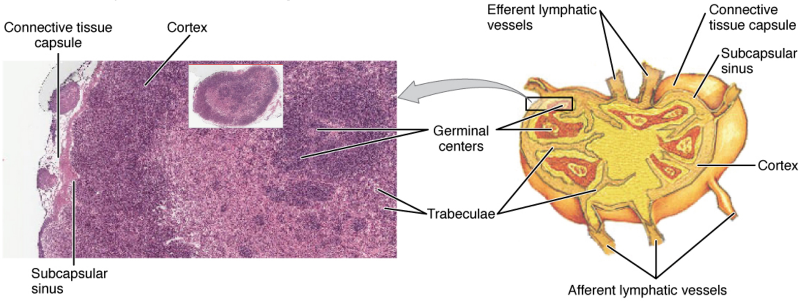
Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph” ([link]). Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

Structure and Histology of a Lymph Node

Lymph nodes are masses of lymphatic tissue located

along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)



View the [University of Michigan WebScope] to explore the tissue sample in greater detail.

The major routes into the lymph node are via **afferent lymphatic vessels** (see [link]). Cells and lymph fluid that leave the lymph node may do so by

another set of vessels known as the **efferent lymphatic vessels**. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

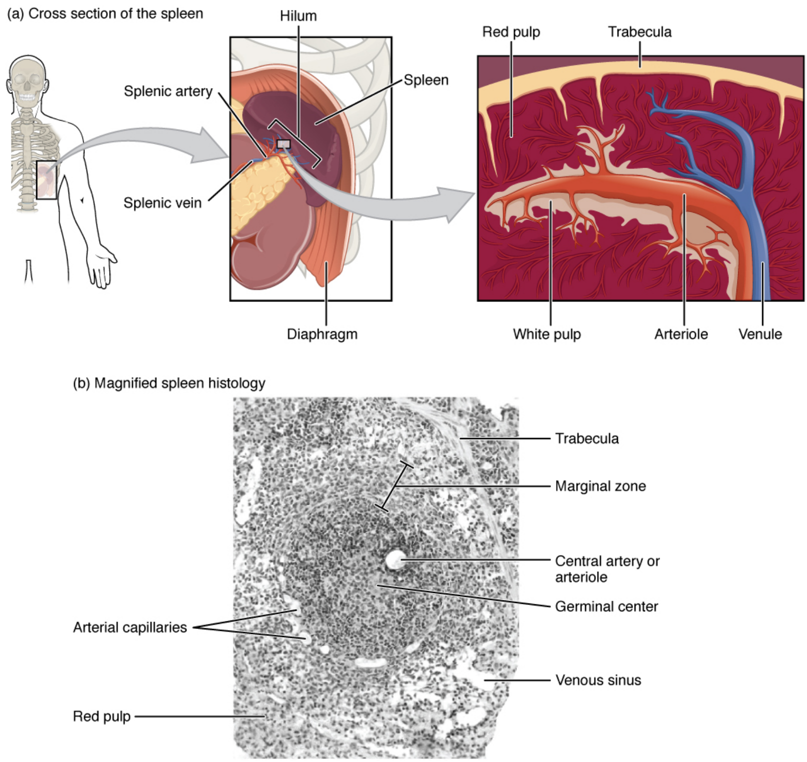
Spleen

In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ ([link]). It is about 12 cm (5 in) long and is attached to the lateral border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the "filter of the blood" because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Spleen

(a) The spleen is attached to the stomach. (b) A

micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)



The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the

spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

Lymphoid Nodules

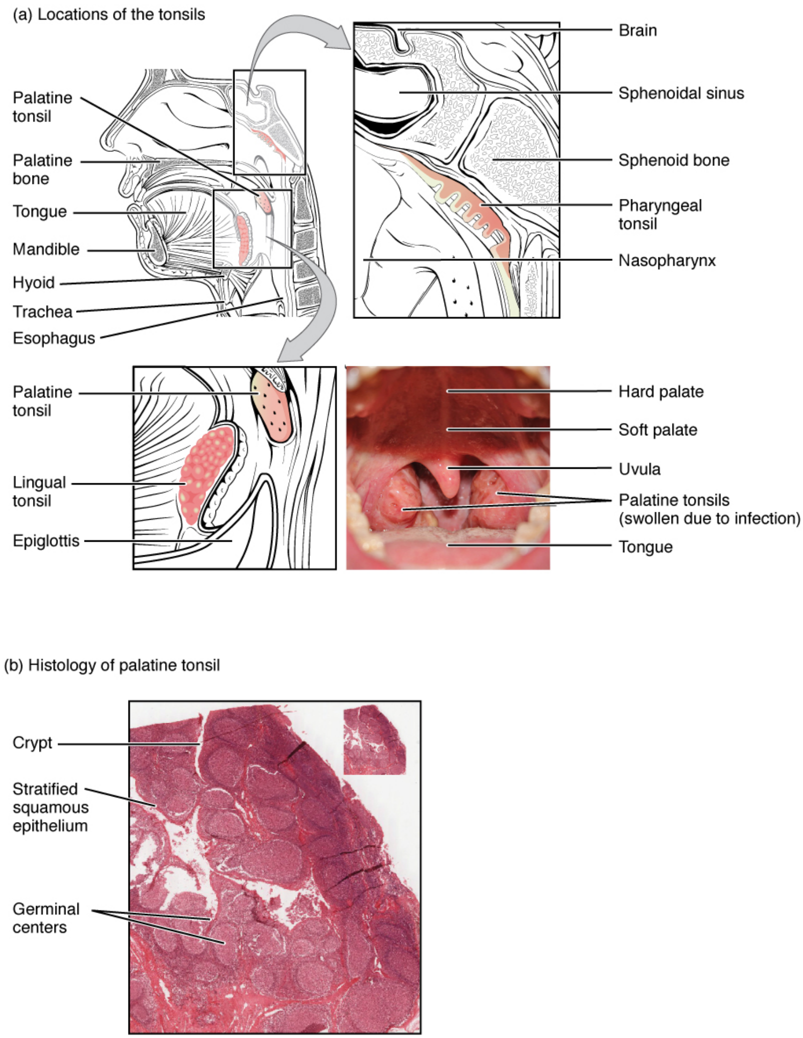
The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens ([link]). The tonsil located at the back of the throat, the

pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children’s bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

Locations and Histology of the Tonsils

(a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM $\times$ 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

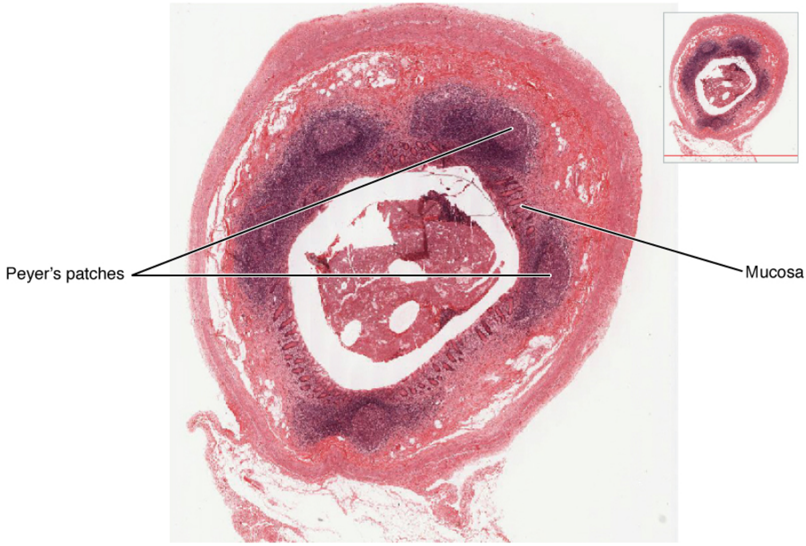

(a) Locations of the tonsils
Brain
Sphenoidal sinus
Sphenoid bone
Pharyngeal tonsil
Nasopharynx
Palatine tonsil
Palatine bone
Tongue
Mandible
Hyoid
Trachea
Esophagus
Palatine tonsil
Lingual tonsil
Epiglottis
Hard palate
Soft palate
Uvula
Palatine tonsils (swollen due to infection)
Tongue
(b) Histology of palatine tonsil
Crypt
Stratified squamous epithelium
Germinal centers

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances ([link]). Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Mucosa-associated Lymphoid Tissue (MALT) Nodule

LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)



Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Chapter Review

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone

marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are site in which mature lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Interactive Link Questions

Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

The three main components are the lymph vessels, the lymph nodes, and the lymph.

Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in infection by HIV?

The dendritic cell transports the virus to a lymph node.

Review Questions

Which of the following cells is phagocytic?

1. plasma cell
2. macrophage
3. B cell
4. NK cell

B

Which structure allows lymph from the lower right limb to enter the bloodstream?

1. thoracic duct
2. right lymphatic duct
3. right lymphatic trunk
4. left lymphatic trunk

A

Which of the following cells is important in the innate immune response?

1. B cells
2. T cells
3. macrophages
4. plasma cells

C

Which of the following cells would be most active in early, antiviral immune responses the first time one is exposed to pathogen?

1. macrophage
2. T cell
3. neutrophil
4. natural killer cell

D

Which of the lymphoid nodules is most likely to see food antigens first?

1. tonsils
2. Peyer's patches
3. bronchus-associated lymphoid tissue
4. mucosa-associated lymphoid tissue

A

Critical Thinking Questions

Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.

The lymph enters through lymphatic capillaries, and then into larger lymphatic vessels. The lymph can only go in one direction due to valves in the vessels. The larger lymphatics merge to form trunks that enter into the blood via lymphatic ducts.

Glossary

adaptive immune response
: relatively slow but very specific and effective immune response controlled by lymphocytes

afferent lymphatic vessels
: lead into a lymph node

antibody
: antigen-specific protein secreted by plasma cells; immunoglobulin

antigen
: molecule recognized by the receptors of B and T lymphocytes

barrier defenses
: antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

B cells
: lymphocytes that act by differentiating into an antibody-secreting plasma cell

bone marrow
: tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)
: lymphoid nodule associated with the respiratory tract

chyle
: lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli
: bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels
: lead out of a lymph node

germinal centers
: clusters of rapidly proliferating B cells found in secondary lymphoid tissues

high endothelial venules
: vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

immune system
: series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response
: rapid but relatively nonspecific immune response

lymph
: fluid contained within the lymphatic system

lymph node
: one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries
: smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system
: network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues

and back to the bloodstream.

lymphatic trunks
: large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes
: white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules
: unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)
: lymphoid nodule associated with the mucosa

naïve lymphocyte
: mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)
: cytotoxic lymphocyte of innate immune response

plasma cell
: differentiated B cell that is actively secreting antibody

primary lymphoid organ
: site where lymphocytes mature and proliferate; red bone marrow and thymus

gland

right lymphatic duct
: drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs
: sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen
: secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell
: lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct
: large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte
: immature T cell found in the thymus

thymus

primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils
: lymphoid nodules associated with the nasopharynx

Barrier Defenses and the Innate Immune Response

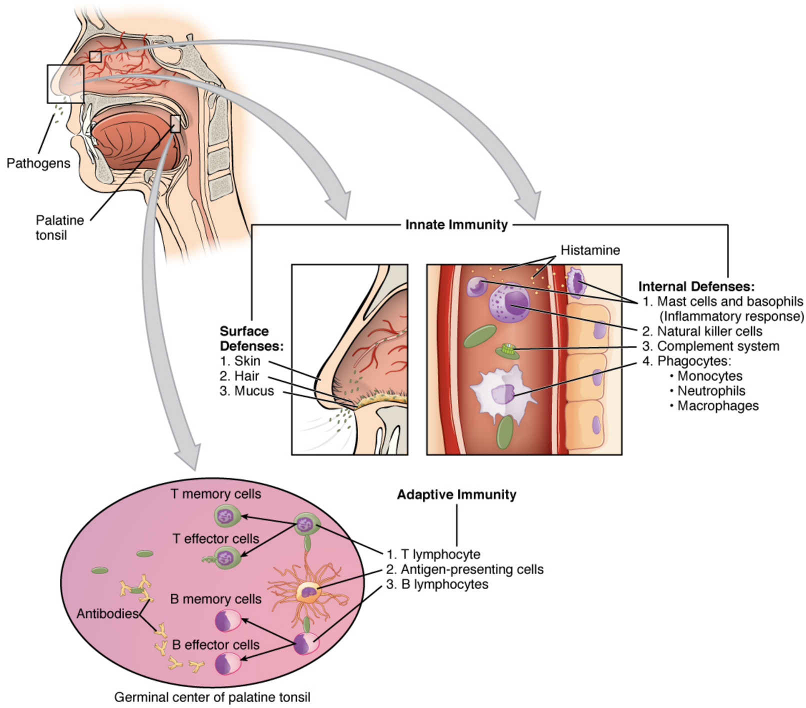
By the end of this section, you will be able to:

- Describe the barrier defenses of the body
- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe various soluble factors that are part of the innate immune response
- Explain the steps of inflammation and how they lead to destruction of a pathogen
- Discuss early induced immune responses and their level of effectiveness

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens ([link]).

Cooperation between Innate and Adaptive Immune Responses

The innate immune system enhances adaptive immune responses so they can be more effective.



Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter ([link]). The primary barrier to the entrance of microorganisms

into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

Barrier Defenses

Site	**Specific defense**	**Protective aspect**
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH
Mucosal surfaces	Mucosal epithelium	Nonkeratinized epithelial cells
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

Another barrier is the saliva in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls. The acidic environment of the stomach, which is fatal to many pathogens, is also a barrier. Additionally, the mucus layer of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable

tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. Macrophages, neutrophils, and dendritic cells are the major phagocytes of the immune system.

A **macrophage** is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body’s barrier defenses,

macrophages are the first line of defense ([link]). They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a macrophage or dendritic cell, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System

Cell	Cell type	Primary location	Function in the innate immune response
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis
Neutrophil	Granulocyte	Blood	Phagocytosis
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals

and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion

of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Early induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

Complement System

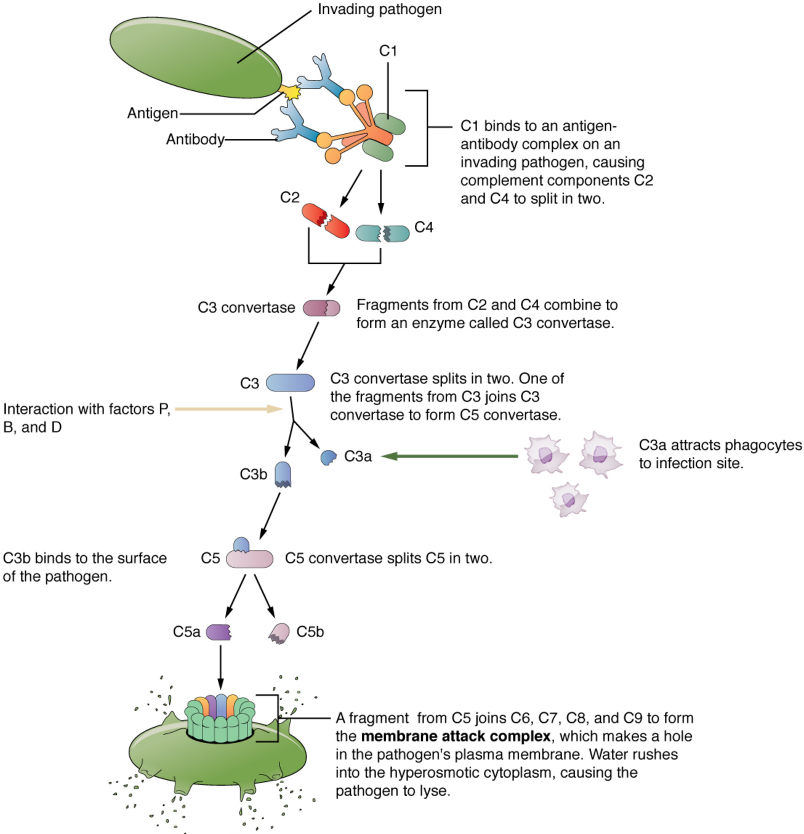
The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the “alternate pathway” of complement activation. Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
- Form damaging pores in the plasma membrane of the pathogen

[link] shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

Complement Cascade and Function

The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.



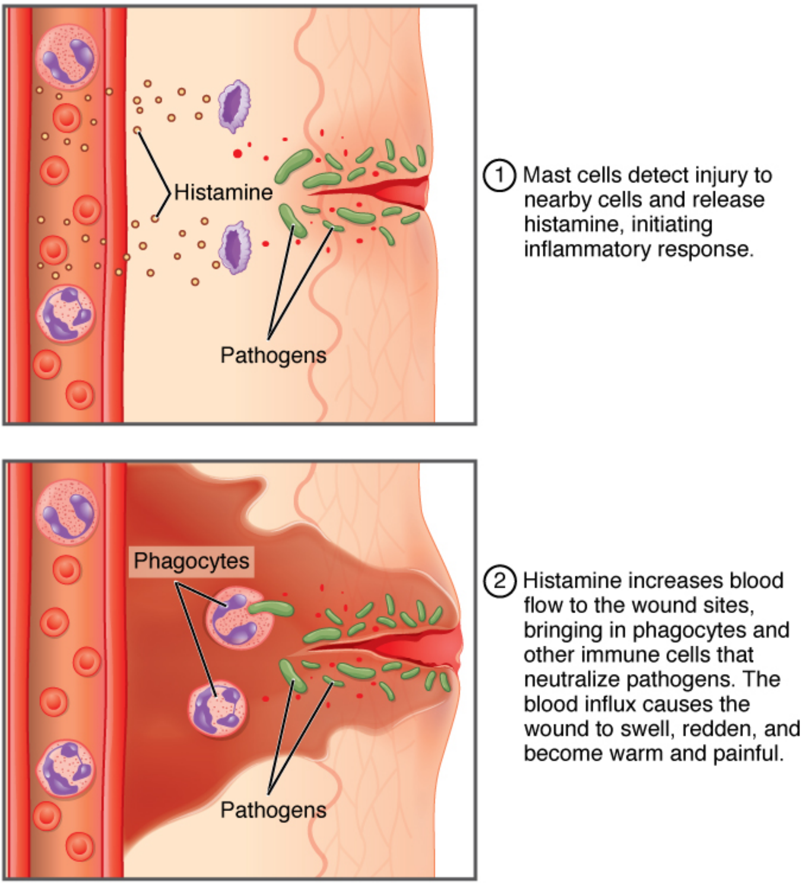
The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade,

with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling ("loss of function" is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of

breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair ([link]).



This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site

to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. **Acute inflammation** is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- *Tissue Injury.* The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation.
  Additionally, injured cells, phagocytes, and basophils are sources of inflammatory mediators, including prostaglandins and leukotrienes. Leukotrienes attract neutrophils from the blood by chemotaxis and increase

vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.

- *Vasodilation.* Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability*. At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.
- *Recruitment of Phagocytes.* Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular

remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally, interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is developed. In fact,

both can cooperate and one can influence the other in their responses against pathogens.

Interactive Link Questions

Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

The bacterium is digested by the phagocyte's digestive enzymes (contained in its lysosomes).

Review Questions

Which of the following signs is *not* characteristic of inflammation?

1. redness
2. pain
3. cold

4. swelling

C

Which of the following is *not* important in the antiviral innate immune response?

1. interferons
2. natural killer cells
3. complement
4. microphages

D

Enhanced phagocytosis of a cell by the binding of a specific protein is called ______.

1. endocytosis
2. opsonization
3. anaphylaxis
4. complement activation

B

Which of the following leads to the redness of inflammation?

1. increased vascular permeability
2. anaphylactic shock
3. increased blood flow
4. complement activation

C

Critical Thinking Questions

Describe the process of inflammation in an area that has been traumatized, but not infected.

The cell debris and damaged cells induce macrophages to begin to clean them up. Macrophages release cytokines that attract neutrophils, followed by more macrophages. Other mediators released by mast cells increase blood flow to the area and also vascular permeability, allowing the recruited cells to get from the blood to the site of infection, where they can phagocytose the dead cells and debris, preparing the site for wound repair.

Describe two early induced responses and what pathogens they affect.

Interferons are produced in virally infected cells and cause them to secrete signals for surrounding cells to make antiviral proteins. C-reactive protein is induced to be made by the liver and will opsonize certain species of bacteria.

Glossary

acute inflammation
: inflammation occurring for a limited time period; rapidly developing

chemokine
: soluble, long-range, cell-to-cell communication molecule

chronic inflammation
: inflammation occurring for long periods of time

complement
: enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine
: soluble, short-range, cell-to-cell communication molecule

early induced immune response

includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand
: molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis

granzyme
: apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine
: vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation
: basic innate immune response characterized by heat, redness, pain, and swelling

interferons
: early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage
: ameboid phagocyte found in several tissues throughout the body

mast cell

cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte
: precursor to macrophages and dendritic cells seen in the blood

neutrophil
: phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization
: enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)
: leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin
: molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis
: movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

Introduction
class="introduction"
Mountain Climbers
The thin air at high elevations can strain the human respiratory system. (credit: “bortescristian”/ flickr.com)

Chapter Objectives

After studying this chapter, you will be able to:

- List the structures of the respiratory system
- List the major functions of the respiratory system
- Outline the forces that allow for air movement into and out of the lungs
- Outline the process of gas exchange
- Summarize the process of oxygen and carbon

dioxide transport within the respiratory system
- Create a flow chart illustrating how respiration is controlled
- Discuss how the respiratory system responds to exercise
- Describe the development of the respiratory system in the embryo

Hold your breath. Really! See how long you can hold your breath as you continue reading…How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product. You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways

through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

Organs and Structures of the Respiratory System

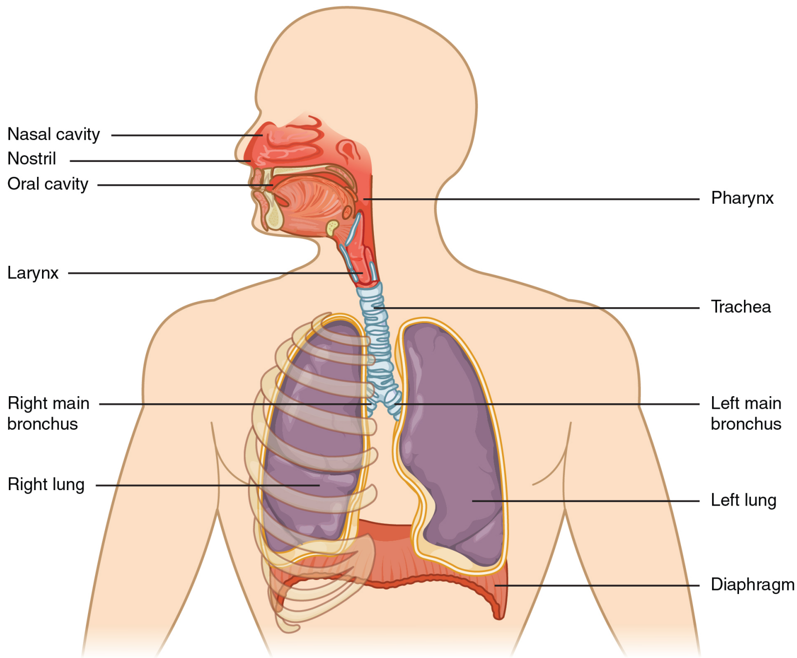
By the end of this section, you will be able to:

- List the structures that make up the respiratory system
- Describe how the respiratory system processes oxygen and CO_2
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing ([link]).

Major Respiratory Structures

The major respiratory structures span the nasal cavity to the diaphragm.



Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other

functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

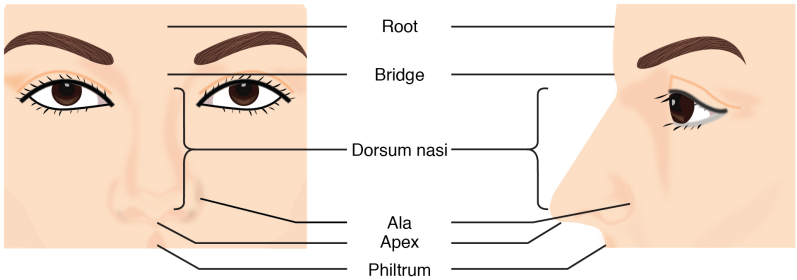
The Nose and its Adjacent Structures

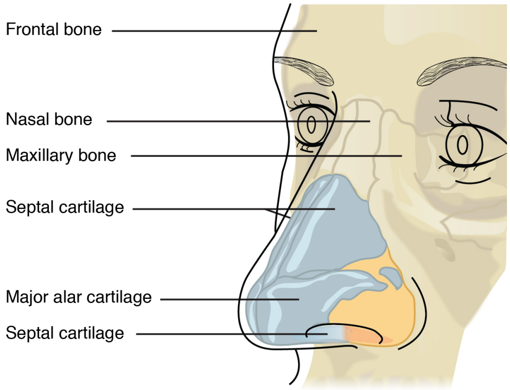
The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The **external nose** consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions ([link]). The **root** is the region of the nose located between the eyebrows. The **bridge** is the part of the nose that connects the root to the rest of the nose. The **dorsum nasi** is the length of the nose. The **apex** is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An **ala** is a cartilaginous structure that forms the lateral side of each **naris** (plural = nares), or nostril opening. The **philtrum** is the concave surface that connects the apex of the nose to the upper lip.

Nose

This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

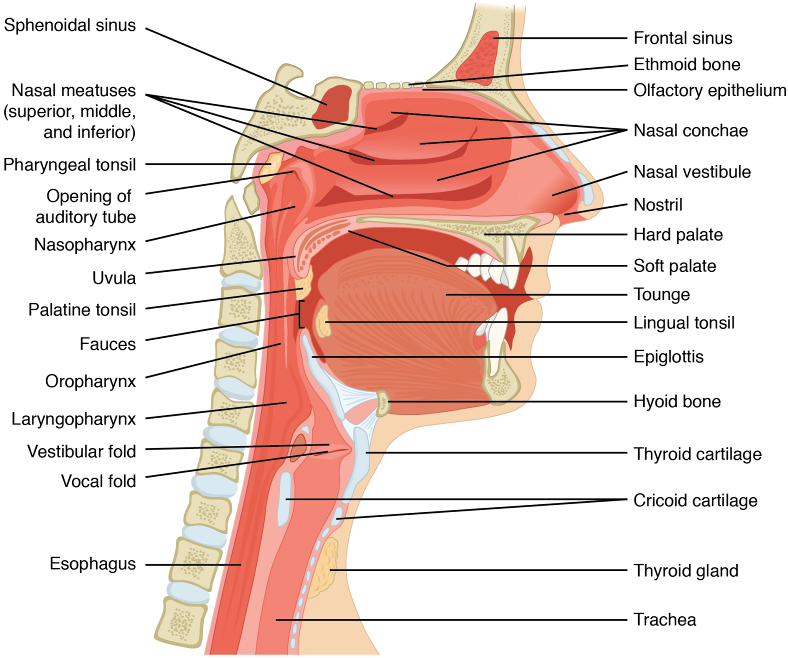




Underneath the thin skin of the nose are its skeletal features (see [link], lower illustration). While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The **nasal bone** is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The **alar cartilage** consists of the apex of the nose; it surrounds the naris.

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum ([link]). The **nasal septum** is formed anteriorly by a portion of the septal cartilage (the flexible portion you can touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae. The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and **meatuses** also conserve water and prevent dehydration of the nasal epithelium by trapping water during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

Upper Airway



Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each **paranasal sinus** is named for its associated bone: frontal sinus, maxillary sinus, sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

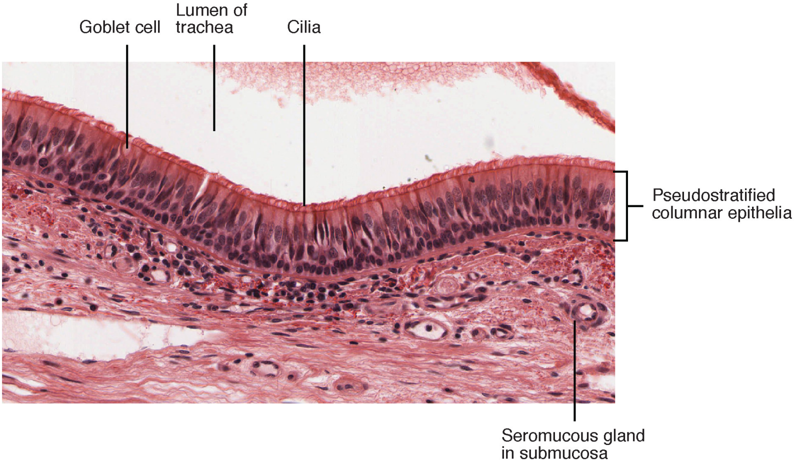
The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal

cavity.

The conchae, meatuses, and paranasal sinuses are lined by **respiratory epithelium** composed of pseudostratified ciliated columnar epithelium ([link]). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

Pseudostratified Ciliated Columnar Epithelium

Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



View the University of Michigan WebScope to explore the tissue sample in greater detail.

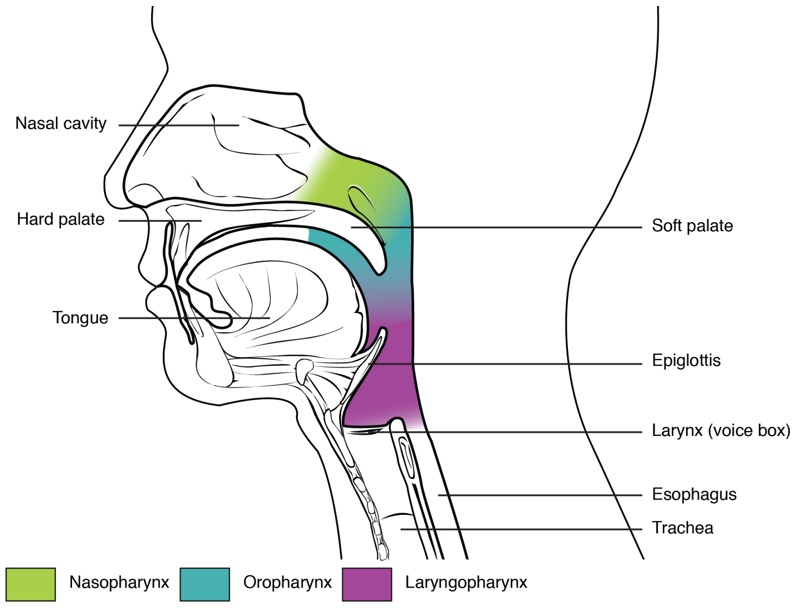
Pharynx

The **pharynx** is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities (see [link]). The

pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx ([link]).

Divisions of the Pharynx

The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.



The **nasopharynx** is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A **pharyngeal tonsil**, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading

pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory (Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

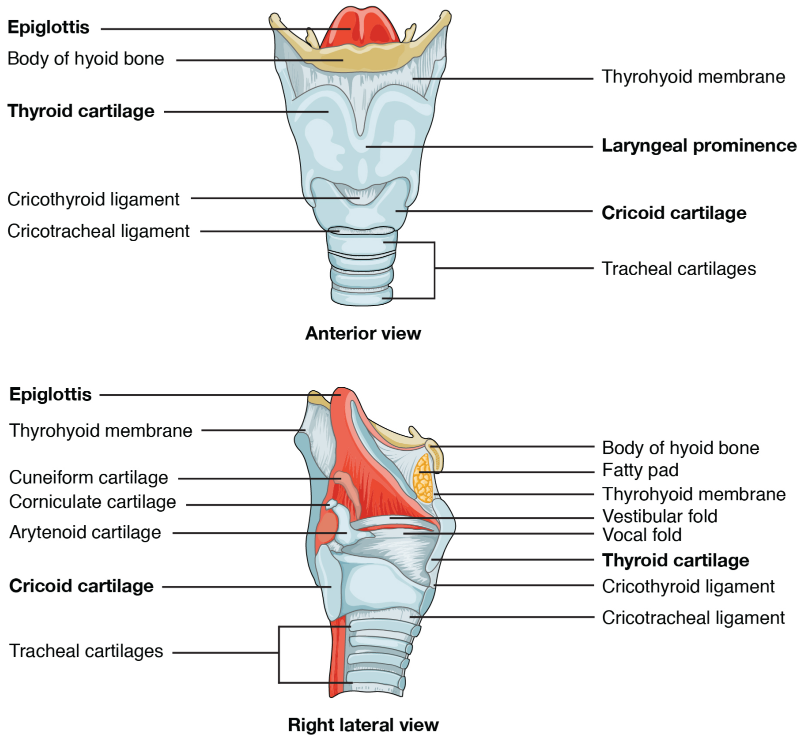
The **oropharynx** is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The **fauces** is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A **palatine tonsil** is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The **lingual tonsil** is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

The **laryngopharynx** is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

Larynx

The **larynx** is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs ([link]). The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The **thyroid cartilage** is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the **laryngeal prominence**, or "Adam's apple," which tends to be more prominent in males. The thick **cricoid cartilage** forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.
Larynx
The larynx extends from the laryngopharynx and

the hyoid bone to the trachea.

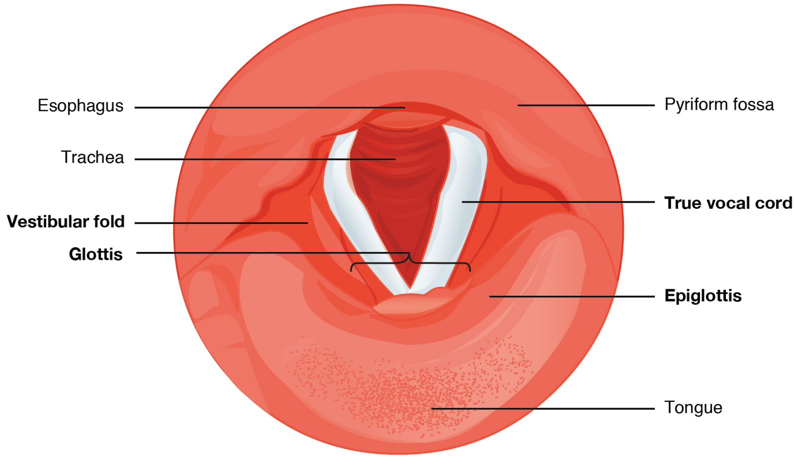


The **epiglottis**, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea (see [link]). When in the "closed" position, the unattached end of the epiglottis rests on the glottis. The **glottis** is composed of the vestibular folds, the true vocal cords, and the space between these folds ([link]). A **vestibular fold**, or false vocal cord, is one of a pair of folded sections of mucous membrane. A **true vocal cord** is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing

oscillation to produce sound. The size of the membranous folds of the true vocal cords differs between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

Vocal Cords

The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.



Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that

contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

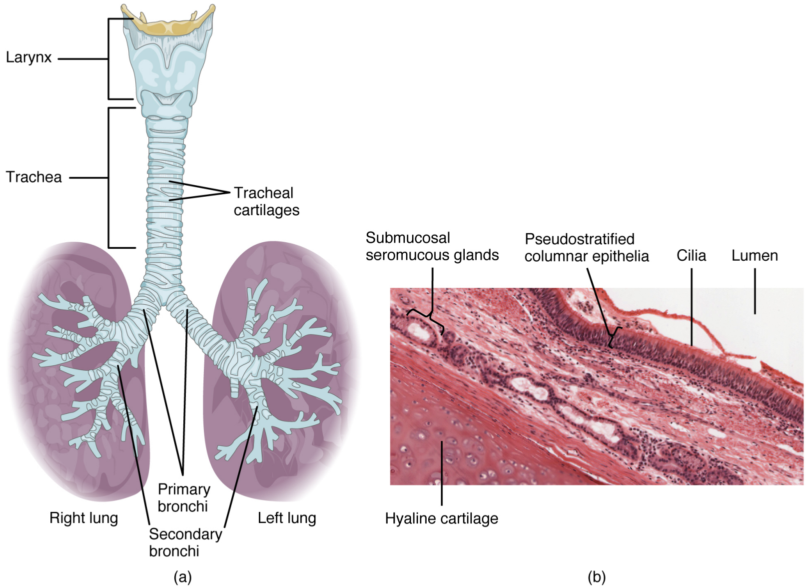
Trachea

The trachea (windpipe) extends from the larynx toward the lungs ([link]**a**). The **trachea** is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

Trachea

(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the

hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Bronchial Tree

The trachea branches into the right and left primary **bronchi** at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells ([link]**b**). The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent

their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A **bronchial tree** (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A **bronchiole** branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

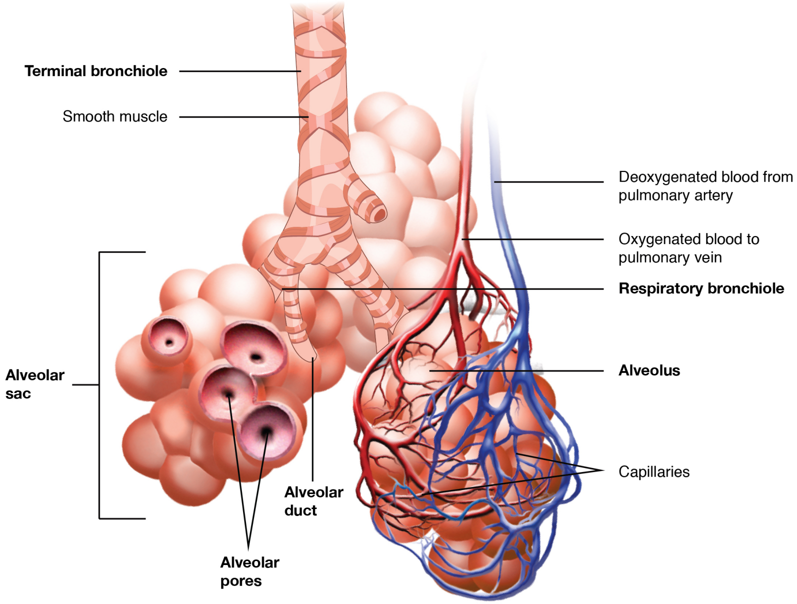
Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole ([link]),

which then leads to an alveolar duct, opening into a cluster of alveoli.

Respiratory Zone

Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.



Alveoli

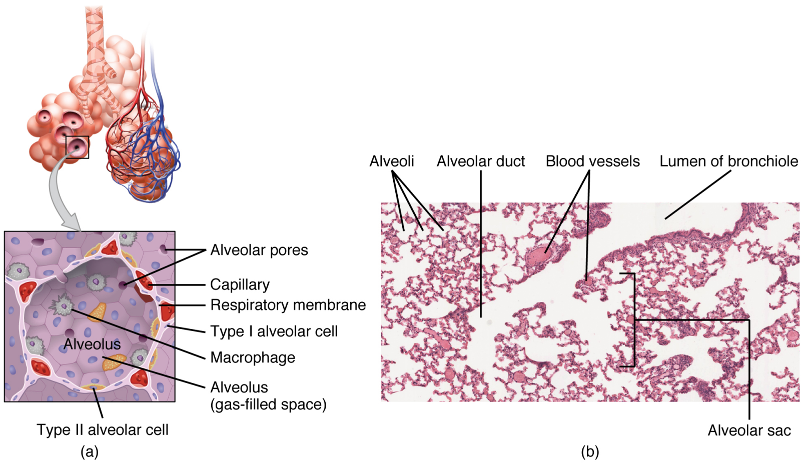
An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 μm in diameter with

elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung ([link]).

Structures of the Respiratory Zone

(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A **type I alveolar cell** is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A **type II alveolar cell** is interspersed among the type I cells and secretes

pulmonary surfactant, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the **alveolar macrophage**, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO_2 to be released into the air of the alveoli.

Diseases of the…

Respiratory System: Asthma

Asthma is common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7 million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children.

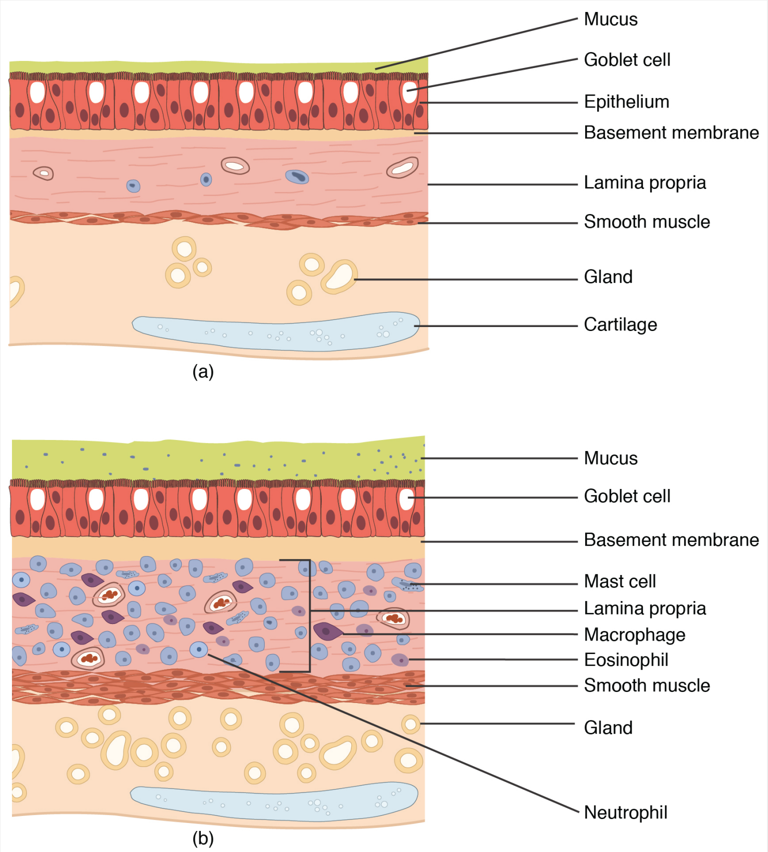
Asthma is a chronic disease characterized by inflammation and edema of the airway, and

bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion ([link]). Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.

Bronchospasms occur periodically and lead to an "asthma attack." An attack may be triggered by environmental factors such as dust, pollen, pet hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.

Normal and Bronchial Asthma Tissues

(a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.



Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used

to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer. In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

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Visit this site to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Chapter Review

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and meatuses that expand the surface area of the cavity, which helps to warm and humidify incoming air, while removing debris and pathogens. The pharynx is composed of three major sections: the nasopharynx, which is continuous with the nasal cavity; the oropharynx, which borders the nasopharynx and the oral cavity; and the laryngopharynx, which borders the oropharynx, trachea, and esophagus. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and

smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

Interactive Link Questions

Visit this site to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Inflammation and the production of a thick mucus; constriction of the airway muscles, or bronchospasm; and an increased sensitivity to allergens.

Review Questions

Which of the following anatomical structures is *not* part of the conducting zone?

1. pharynx
2. nasal cavity
3. alveoli
4. bronchi

C

What is the function of the conchae in the nasal cavity?

1. increase surface area
2. exchange gases
3. maintain surface tension
4. maintain air pressure

A

The fauces connects which of the following structures to the oropharynx?

1. nasopharynx
2. laryngopharynx
3. nasal cavity
4. oral cavity

D

Which of the following are structural features of the trachea?

1. C-shaped cartilage
2. smooth muscle fibers
3. cilia
4. all of the above

A

Which of the following structures is *not* part of the bronchial tree?

1. alveoli
2. bronchi
3. terminal bronchioles
4. respiratory bronchioles

C

What is the role of alveolar macrophages?

1. to secrete pulmonary surfactant
2. to secrete antimicrobial proteins
3. to remove pathogens and debris
4. to facilitate gas exchange

C

Critical Thinking Questions

Describe the three regions of the pharynx and their functions.

The pharynx has three major regions. The first region is the nasopharynx, which is connected to the posterior nasal cavity and functions as an airway. The second region is the oropharynx, which is continuous with the nasopharynx and is connected to the oral cavity at the fauces. The laryngopharynx is connected to the oropharynx and the esophagus and trachea. Both the oropharynx and laryngopharynx are passageways for air and food and drink.

If a person sustains an injury to the epiglottis, what would be the physiological result?

The epiglottis is a region of the larynx that is important during the swallowing of food or drink. As a person swallows, the pharynx moves upward and the epiglottis closes over the

trachea, preventing food or drink from entering the trachea. If a person’s epiglottis were injured, this mechanism would be impaired. As a result, the person may have problems with food or drink entering the trachea, and possibly, the lungs. Over time, this may cause infections such as pneumonia to set in.

Compare and contrast the conducting and respiratory zones.

The conducting zone of the respiratory system includes the organs and structures that are not directly involved in gas exchange, but perform other duties such as providing a passageway for air, trapping and removing debris and pathogens, and warming and humidifying incoming air. Such structures include the nasal cavity, pharynx, larynx, trachea, and most of the bronchial tree. The respiratory zone includes all the organs and structures that are directly involved in gas exchange, including the respiratory bronchioles, alveolar ducts, and alveoli.

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Glossary

ala
: (plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

alar cartilage
: cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

alveolar duct
: small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage
: immune system cell of the alveolus that removes debris and pathogens

alveolar pore
: opening that allows airflow between neighboring alveoli

alveolar sac
: cluster of alveoli

alveolus
: small, grape-like sac that performs gas exchange in the lungs

apex
: tip of the external nose

bronchial tree
: collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bridge
: portion of the external nose that lies in the area of the nasal bones

bronchiole

branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchus
: tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

conducting zone
: region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

cricoid cartilage
: portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

dorsum nasi
: intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

epiglottis
: leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

external nose

region of the nose that is easily visible to others

fauces
: portion of the posterior oral cavity that connects the oral cavity to the oropharynx

fibroelastic membrane
: specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

glottis
: opening between the vocal folds through which air passes when producing speech

laryngeal prominence
: region where the two lamina of the thyroid cartilage join, forming a protrusion known as "Adam's apple"

laryngopharynx
: portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food

larynx
: cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

lingual tonsil
: lymphoid tissue located at the base of the tongue

meatus
: one of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity

naris
: (plural = nares) opening of the nostrils

nasal bone
: bone of the skull that lies under the root and bridge of the nose and is connected to the frontal and maxillary bones

nasal septum
: wall composed of bone and cartilage that separates the left and right nasal cavities

nasopharynx
: portion of the pharynx flanked by the conchae and oropharynx that serves as an airway

oropharynx
: portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food

palatine tonsil

one of the paired structures composed of lymphoid tissue located anterior to the uvula at the roof of isthmus of the fauces

paranasal sinus

one of the cavities within the skull that is connected to the conchae that serve to warm and humidify incoming air, produce mucus, and lighten the weight of the skull; consists of frontal, maxillary, sphenoidal, and ethmoidal sinuses

pharyngeal tonsil

structure composed of lymphoid tissue located in the nasopharynx

pharynx

region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

philtrum

concave surface of the face that connects the apex of the nose to the top lip

pulmonary surfactant

substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

respiratory bronchiole
: specific type of bronchiole that leads to alveolar sacs

respiratory epithelium
: ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane
: alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory zone
: includes structures of the respiratory system that are directly involved in gas exchange

root
: region of the external nose between the eyebrows

thyroid cartilage
: largest piece of cartilage that makes up the larynx and consists of two lamina

trachea
: tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

trachealis muscle
: smooth muscle located in the fibroelastic membrane of the trachea

true vocal cord
: one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

type I alveolar cell
: squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell
: cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

vestibular fold
: part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

Gas Exchange

By the end of this section, you will be able to:

- Compare the composition of atmospheric air and alveolar air
- Describe the mechanisms that drive gas exchange
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Describe the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their

behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

Gas Laws and Air Composition

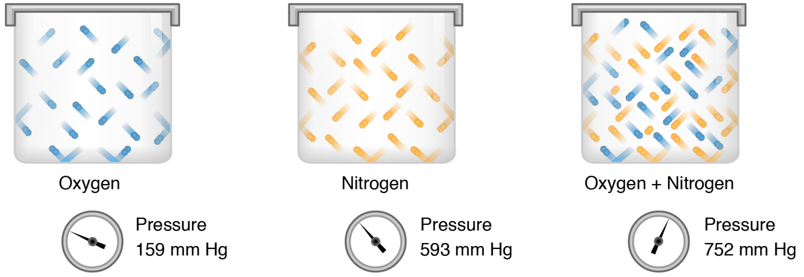
Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure ([link]). **Partial pressure** (P_x) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen ([link]). **Total pressure** is the sum of all the partial pressures of a gaseous mixture. **Dalton's law** describes the behavior of nonreactive gases in a gaseous mixture and states that a specific gas type in a mixture exerts its own pressure; thus, the total pressure exerted by a mixture of gases is the sum of the partial pressures of the gases in the mixture.

Partial Pressures of Atmospheric Gases

Gas	Percent of total composition	Partial pressure (mm Hg)
Nitrogen (N_2)	78.6	597.4
Oxygen (O_2)	20.9	158.8
Water (H_2O)	0.4	3.0
Carbon dioxide (CO_2)	0.04	0.3
Others	0.06	0.5
Total composition/total atmospheric pressure	100%	760.0

Partial and Total Pressures of a Gas

Partial pressure is the force exerted by a gas. The sum of the partial pressures of all the gases in a mixture equals the total pressure.



Partial pressure is extremely important in predicting the movement of gases. Recall that gases tend to equalize their pressure in two regions that are

connected. A gas will move from an area where its partial pressure is higher to an area where its partial pressure is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases.

Solubility of Gases in Liquids

Henry's law describes the behavior of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low. The exception to this occurs in scuba divers; the composition of the compressed air that divers breathe causes nitrogen to have a higher partial pressure than normal, causing it to dissolve in the blood in greater amounts than normal. Too much nitrogen in the bloodstream results in a serious condition that can be fatal if not corrected. Gas molecules establish an equilibrium between those molecules dissolved in liquid and those in air.

The composition of air in the atmosphere and in the

alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air ([link]). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

Composition and Partial Pressures of Alveolar Air

Gas	Percent of total composition	Partial pressure (mm Hg)

Nitrogen (N_2)	74.9	569
Oxygen (O_2)	13.7	104
Water (H_2O)	6.2	40
Carbon dioxide (CO_2)	5.2	47
Total composition/ total alveolar pressure	100%	760.0

Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of oxygenated blood in pulmonary veins is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the

large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serves the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

Gas Exchange

Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

External Respiration

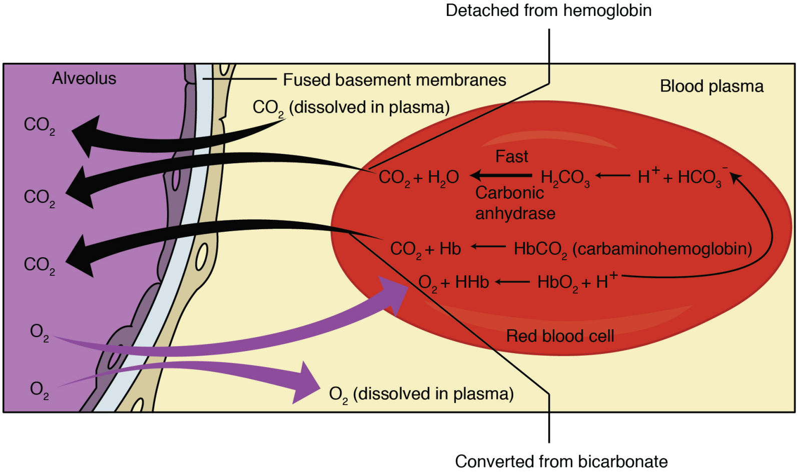
The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the

alveoli ([link]). As the blood is pumped through this capillary network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

External respiration occurs as a function of partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.

External Respiration

In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.



Although the solubility of oxygen in blood is not high, there is a drastic difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries. This difference is about 64 mm Hg: The partial pressure of oxygen in the alveoli is about 104 mm Hg, whereas its partial pressure in the blood of the capillary is about 40 mm Hg. This large difference in partial pressure creates a very strong pressure gradient that causes oxygen to rapidly cross the respiratory membrane from the alveoli into the blood.

The partial pressure of carbon dioxide is also different between the alveolar air and the blood of the capillary. However, the partial pressure difference is less than that of oxygen, about 5 mm Hg. The partial pressure of carbon dioxide in the blood of the capillary is about 45 mm Hg, whereas its partial pressure in the alveoli is about 40 mm Hg. However, the solubility of carbon dioxide is much

greater than that of oxygen—by a factor of about 20—in both blood and alveolar fluids. As a result, the relative concentrations of oxygen and carbon dioxide that diffuse across the respiratory membrane are similar.

Internal Respiration

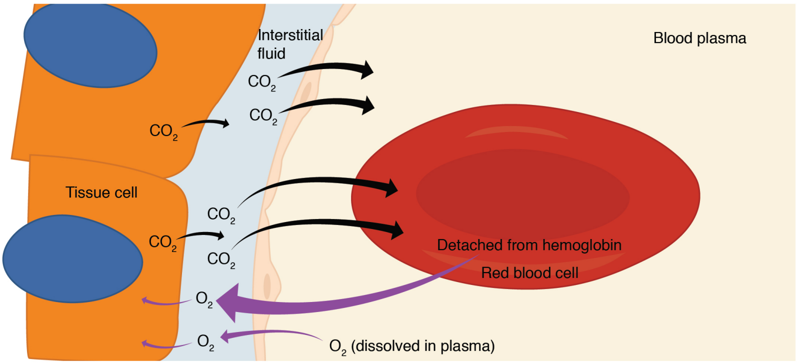
Internal respiration is gas exchange that occurs at the level of body tissues ([link]). Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the respiratory membrane. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used for cellular respiration. In contrast, the partial pressure of oxygen in the blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either

bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure of carbon dioxide has returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

Internal Respiration

Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.



Everyday Connection

Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric

air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically for one patient, and the staff tending to the patient observes the patient from outside of the chamber ([link]). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.

Hyperbaric Chamber

(credit: “komunews”/flickr.com)

Hyperbaric chamber treatment is based on the behavior of gases. As you recall, gases move from a region of higher partial pressure to a region of lower partial pressure. In a hyperbaric chamber, the atmospheric pressure is increased, causing a greater amount of oxygen than normal to diffuse into the bloodstream of the patient. Hyperbaric chamber therapy is used to treat a variety of medical problems, such as wound and graft healing, anaerobic bacterial infections, and carbon monoxide poisoning. Exposure to and poisoning by carbon monoxide is difficult to reverse, because hemoglobin’s affinity for carbon monoxide is much stronger than its affinity for oxygen, causing carbon monoxide to replace oxygen in the blood. Hyperbaric chamber therapy can treat carbon monoxide poisoning, because the increased atmospheric pressure causes more oxygen to diffuse into the bloodstream. At this increased pressure and increased concentration of oxygen, carbon monoxide is displaced from hemoglobin. Another example is the treatment of anaerobic bacterial infections, which are created by bacteria that cannot or prefer not to live in the presence of oxygen. An increase in blood and tissue levels of oxygen helps to kill the anaerobic bacteria that are responsible for the infection, as oxygen is toxic to anaerobic bacteria. For wounds and grafts, the chamber stimulates the healing process by increasing energy production needed for repair. Increasing oxygen transport allows cells to ramp up

cellular respiration and thus ATP production, the energy needed to build new structures.

Chapter Review

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon

dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

Review Questions

Gas moves from an area of ______ partial pressure to an area of ______ partial pressure.

1. low; high
2. low; low
3. high; high
4. high; low

D

When ventilation is not sufficient, which of the following occurs?

1. The capillary constricts.
2. The capillary dilates.
3. The partial pressure of oxygen in the affected alveolus increases.
4. The bronchioles dilate.

A

Gas exchange that occurs at the level of the tissues is called _____.

1. external respiration
2. interpulmonary respiration
3. internal respiration
4. pulmonary ventilation

C

The partial pressure of carbon dioxide is 45 mm Hg in the blood and 40 mm Hg in the alveoli. What happens to the carbon dioxide?

1. It diffuses into the blood.
2. It diffuses into the alveoli.

3. The gradient is too small for carbon dioxide to diffuse.
4. It decomposes into carbon and oxygen.

B

Critical Thinking Questions

Compare and contrast Dalton's law and Henry's law.

Both Dalton's and Henry's laws describe the behavior of gases. Dalton's law states that any gas in a mixture of gases exerts force as if it were not in a mixture. Henry's law states that gas molecules dissolve in a liquid proportional to their partial pressure.

A smoker develops damage to several alveoli that then can no longer function. How does this affect gas exchange?

The damaged alveoli will have insufficient ventilation, causing the partial pressure of oxygen in the alveoli to decrease. As a result,

the pulmonary capillaries serving these alveoli will constrict, redirecting blood flow to other alveoli that are receiving sufficient ventilation.

Glossary

Dalton's law
: statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

external respiration
: gas exchange that occurs in the alveoli

Henry's law
: statement of the principle that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas

internal respiration
: gas exchange that occurs at the level of body tissues

partial pressure
: force exerted by each gas in a mixture of gases

total pressure
: sum of all the partial pressures of a gaseous

mixture

ventilation
: movement of air into and out of the lungs; consists of inspiration and expiration

Introduction
class="introduction"
Eating Apples
Eating may be one of the simple pleasures in life, but digesting even one apple requires the coordinated work of many organs. (credit: “Aimanness Photography”/Flickr)


Chapter Objectives
After studying this chapter, you will be able to:

- List and describe the functional anatomy of the organs and accessory organs of the digestive system
- Discuss the processes and control of ingestion,

propulsion, mechanical digestion, chemical digestion, absorption, and defecation
- Discuss the roles of the liver, pancreas, and gallbladder in digestion
- Compare and contrast the digestion of the three macronutrients

The digestive system is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple's taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don't notice that your digestive system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple. In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

Overview of the Digestive System

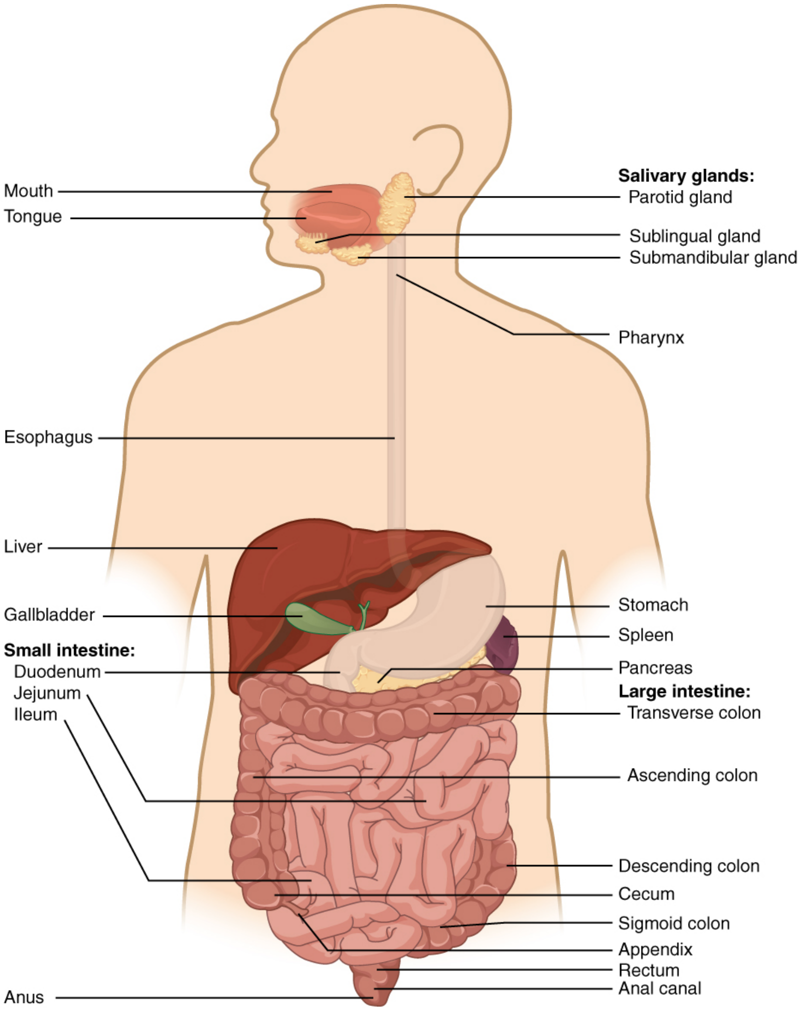
By the end of this section, you will be able to:

- Identify the organs of the alimentary canal from proximal to distal, and briefly state their function
- Identify the accessory digestive organs and briefly state their function
- Describe the four fundamental tissue layers of the alimentary canal
- Contrast the contributions of the enteric and autonomic nervous systems to digestive system functioning
- Explain how the peritoneum anchors the digestive organs

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process ([link]).

Components of the Digestive System

All digestive organs play integral roles in the life-sustaining process of digestion.



As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic

portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. [link] gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Contribution of Other Body Systems to the Digestive System

Body system	Benefits received by the digestive system
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients
Endocrine	Endocrine hormones help

	regulate secretion in digestive glands and accessory organs
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream
Muscular	Skeletal muscles support and protect abdominal organs
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide
Skeletal	Bones help protect and support digestive organs
Urinary	Kidneys convert vitamin D into its active form, allowing calcium

absorption in the small intestine

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the **alimentary canal** (aliment- = "to nourish") is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and large intestines to fit the functional needs

of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

Accessory Structures

Each **accessory digestive organ** aids in the breakdown of food ([link]). Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

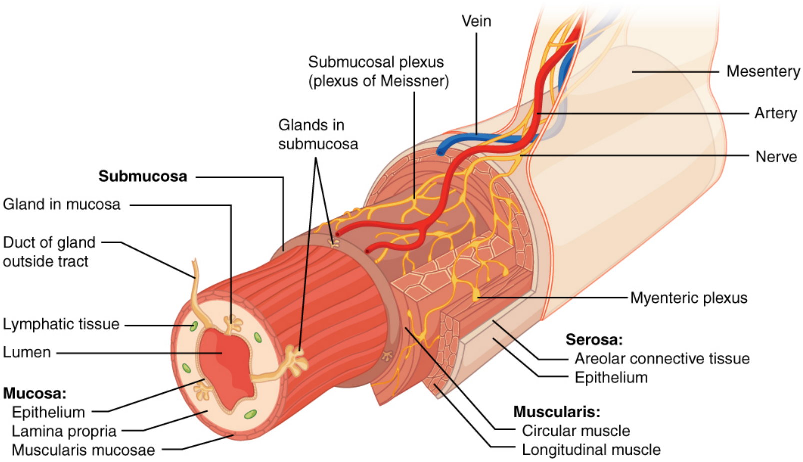
Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details

of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (see [link]).

Layers of the Alimentary Canal

The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.



The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosa (not to be confused with the muscularis layer, described below).

Epithelium—In the mouth, pharynx, esophagus, and

anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer’s patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosa—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscularis** (also called the muscularis externa). The muscularis in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter, the muscularis is made up of skeletal muscle, which gives you voluntary control over

swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer is segregated into three narrow parallel bands, the tenia coli, which make it look like a series of pouches rather than a simple tube.

The **serosa** is the portion of the alimentary canal superficial to the muscularis. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action

enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The **myenteric plexus** (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for **motility**, especially the rhythm and force of the contractions of the muscularis. The **submucosal plexus** (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food (see [link]).

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are "resting and digesting," about one-fourth of the blood pumped with each heartbeat

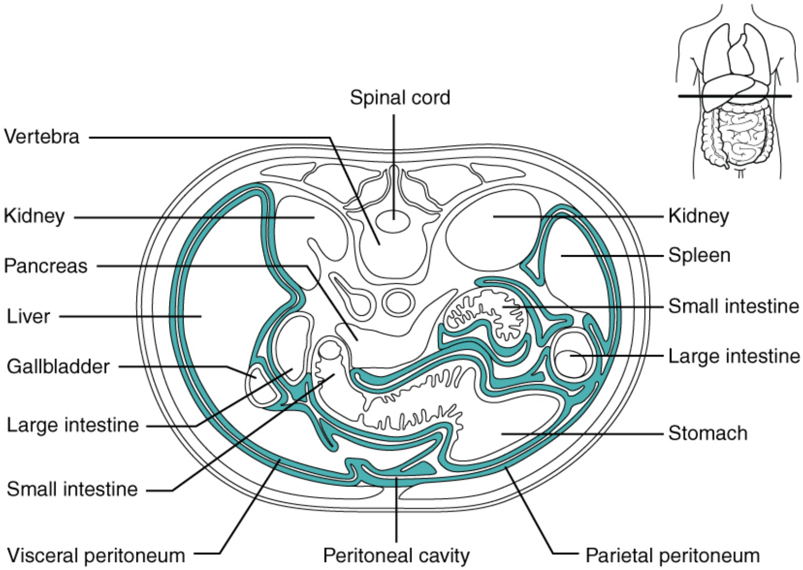
enters arteries serving the intestines.

The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs ([link]). The peritoneal cavity is the space bounded by the visceral and parietal peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

The Peritoneum

A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).



Disorders of the…

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually transmitted bacteria).

Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in [link]. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

The Five Major Peritoneal Folds

Fold	Description
Greater omentum	Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight
Falciform ligament	Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm
Lesser omentum	Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver
Mesentery	Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum)
Mesocolon	Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall

By clicking on this link you can watch a short video of what happens to the food you eat, as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Chapter Review

The digestive system includes the organs of the alimentary canal and accessory structures. The alimentary canal forms a continuous tube that is open to the outside environment at both ends. The organs of the alimentary canal are the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory digestive structures include the teeth, tongue, salivary glands, liver, pancreas, and gallbladder. The wall of the alimentary canal is composed of four basic tissue

layers: mucosa, submucosa, muscularis, and serosa. The enteric nervous system provides intrinsic innervation, and the autonomic nervous system provides extrinsic innervation.

Interactive Link Questions

By clicking on this link, you can watch a short video of what happens to the food you eat as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Answers may vary.

Review Questions

Which of these organs is not considered an accessory digestive structure?

1. mouth
2. salivary glands
3. pancreas

4. liver

A

Which of the following organs is supported by a layer of adventitia rather than serosa?

1. esophagus
2. stomach
3. small intestine
4. large intestine

A

Which of the following membranes covers the stomach?

1. falciform ligament
2. mesocolon
3. parietal peritoneum
4. visceral peritoneum

D

Critical Thinking Questions

Explain how the enteric nervous system supports the digestive system. What might occur that could result in the autonomic nervous system having a negative impact on digestion?

The enteric nervous system helps regulate alimentary canal motility and the secretion of digestive juices, thus facilitating digestion. If a person becomes overly anxious, sympathetic innervation of the alimentary canal is stimulated, which can result in a slowing of digestive activity.

What layer of the alimentary canal tissue is capable of helping to protect the body against disease, and through what mechanism?

The lamina propria of the mucosa contains lymphoid tissue that makes up the MALT and responds to pathogens encountered in the alimentary canal.

Glossary

accessory digestive organ

includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

alimentary canal
: continuous muscular digestive tube that extends from the mouth to the anus

motility
: movement of food through the GI tract

mucosa
: innermost lining of the alimentary canal

muscularis
: muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus
: (plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

retroperitoneal
: located posterior to the peritoneum

serosa
: outermost layer of the alimentary canal wall present in regions within the abdominal cavity

submucosa
: layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

submucosal plexus

(plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

Digestive System Processes and Regulation

By the end of this section, you will be able to:

- Discuss six fundamental activities of the digestive system, giving an example of each
- Compare and contrast the neural and hormonal controls involved in digestion

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. [link] provides an overview of the basic functions of the digestive organs.

Visit this site for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**
Mouth	Ingests food Chews and mixes food Begins chemical breakdown of carbohydrates Moves food into the pharynx Begins breakdown of lipids via lingual lipase	Moistens and dissolves food, allowing you to taste it Cleans and lubricates the teeth and oral cavity Has some antimicrobial activity
Pharynx	Propels food from the oral cavity to the esophagus	Lubricates food and passageways
Esophagus	Propels food to the stomach	Lubricates food and passageways
Stomach	Mixes and churns food with gastric juices to form chyme Begins chemical breakdown of proteins Releases food into the duodenum as chyme Absorbs some fat-soluble substances (for example, alcohol, aspirin) Possesses antimicrobial functions	Stimulates protein-digesting enzymes Secretes intrinsic factor required for vitamin B12 absorption in small intestine
Small intestine	Mixes chyme with digestive juices Propels food at a rate slow enough for digestion and absorption Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water Performs physical digestion via segmentation	Provides optimal medium for enzymatic activity

Accessory organs	Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption Gallbladder: stores, concentrates, and releases bile Pancreas: produces digestive enzymes and bicarbonate	Bicarbonate-rich pancreatic juice helps neutralize acidic chyme and provide optimal environment for enzymatic activity
Large intestine	Further breakdown of food residues Absorption of most residual water, electrolytes, and vitamins produced by enteric bacteria Propels feces toward rectum Eliminates feces	Food residue is concentrated and temporarily stored prior to defecation Mucus eases passage of feces through colon

Digestive Processes

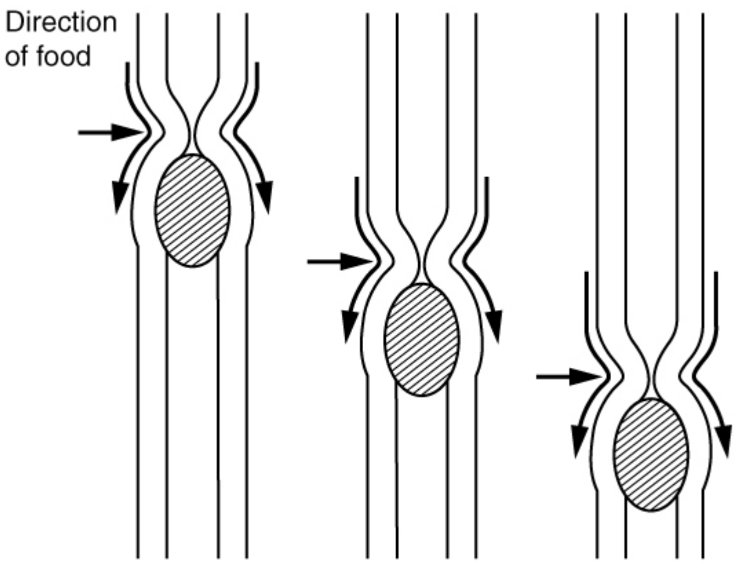
The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and defecation.

The first of these processes, **ingestion**, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of **propulsion**, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. **Peristalsis** consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along ([link]). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Peristalsis

Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.



Digestion includes both mechanical and chemical processes. **Mechanical digestion** is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes **mastication**, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called **chyme**. **Segmentation**, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In **chemical digestion**, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The

process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of **absorption**, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In **defecation**, the final step in digestion, undigested materials are removed from the body as feces.

Aging and the…

Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn’t as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren’t producing enough saliva. Swallowing can be difficult, and ingested

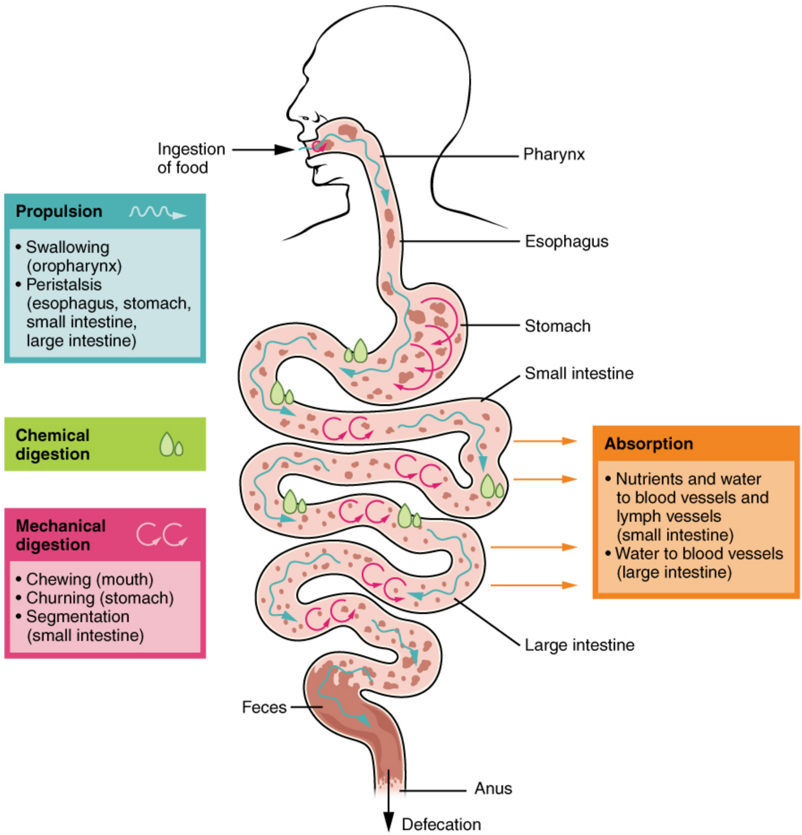
food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal ([link]).

Digestive Processes

The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.



Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for digestion and absorption. These regulatory mechanisms, which stimulate digestive

activity through mechanical and chemical activity, are controlled both extrinsically and intrinsically.

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses

orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone of the stomach is gastrin, which is secreted in response to the presence of food. Gastrin stimulates the secretion of gastric acid by the parietal cells of the stomach mucosa. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum include secretin, which stimulates a watery secretion of bicarbonate by the

pancreas; cholecystokinin (CCK), which stimulates the secretion of pancreatic enzymes and bile from the liver and release of bile from the gallbladder; and gastric inhibitory peptide, which inhibits gastric secretion and slows gastric emptying and motility. These GI hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. These hormones then enter the bloodstream, through which they can reach their target organs.

Chapter Review

The digestive system ingests and digests food, absorbs released nutrients, and excretes food components that are indigestible. The six activities involved in this process are ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. These processes are regulated by neural and hormonal mechanisms.

Interactive Link Questions

Visit this site for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the

small intestine to their release as nutrients to the body.

Answers may vary.

Multiple Choice

Which of these processes occurs in the mouth?

1. ingestion
2. mechanical digestion
3. chemical digestion
4. all of the above

D

Which of these processes occurs throughout most of the alimentary canal?

1. ingestion
2. propulsion
3. segmentation
4. absorption

B

Which of the following stimuli activates sensors in the walls of digestive organs?

1. breakdown products of digestion
2. distension
3. pH of chyme
4. all of the above

D

Which of these statements about reflexes in the GI tract is false?

1. Short reflexes are provoked by nerves near the GI tract.
2. Short reflexes are mediated by the enteric nervous system.
3. Food that distends the stomach initiates long reflexes.
4. Long reflexes can be provoked by stimuli originating outside the GI tract.

C

Critical Thinking Questions

Offer a theory to explain why segmentation occurs and peristalsis slows in the small intestine.

The majority of digestion and absorption occurs in the small intestine. By slowing the transit of chyme, segmentation and a reduced rate of peristalsis allow time for these processes to occur.

It has been several hours since you last ate. Walking past a bakery, you catch a whiff of freshly baked bread. What type of reflex is triggered, and what is the result?

The smell of food initiates long reflexes, which result in the secretion of digestive juices.

Glossary

absorption
: passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

chemical digestion
: enzymatic breakdown of food

chyme
: soupy liquid created when food is mixed with digestive juices

defecation
: elimination of undigested substances from the body in the form of feces

ingestion
: taking food into the GI tract through the mouth

mastication
: chewing

mechanical digestion
: chewing, mixing, and segmentation that prepares food for chemical digestion

peristalsis
: muscular contractions and relaxations that propel food through the GI tract

propulsion
: voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

segmentation
: alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it

apart and mixing it with digestive juices

The Stomach

By the end of this section, you will be able to:

- Label on a diagram the four main regions of the stomach, its curvatures, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at

holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

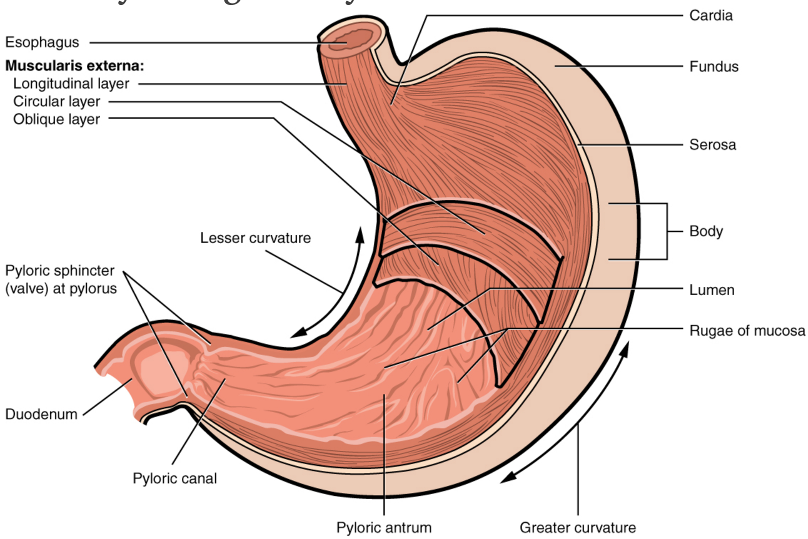
Structure

There are four main regions in the **stomach**: the cardia, fundus, body, and pylorus ([link]). The **cardia** (or cardiac region) is the point where the esophagus connects to the stomach and through

which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach. The funnel-shaped **pylorus** connects the stomach to the duodenum. The wider end of the funnel, the **pyloric antrum**, connects to the body of the stomach. The narrower end is called the **pyloric canal**, which connects to the duodenum. The smooth muscle **pyloric sphincter** is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a **ruga**.

Stomach

The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.



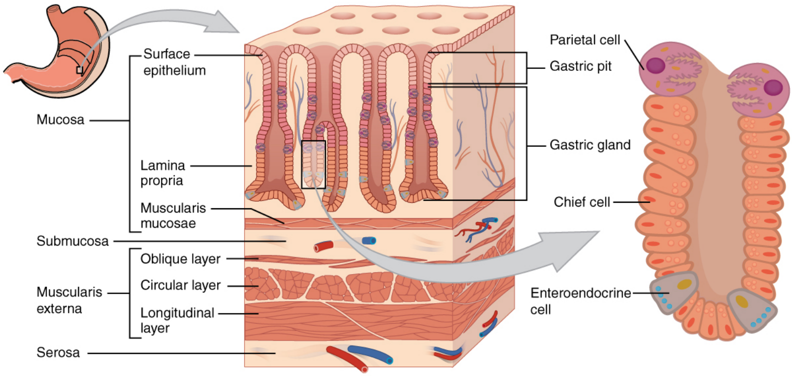
The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer ([link]). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.

Histology of the Stomach

The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.



The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric pits** dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located primarily in the middle region of the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B_{12} in the small intestine.

Chief cells—Located primarily in the basal regions of gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina

propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

[link] describes the digestive functions of important hormones secreted by the stomach.

Watch this animation that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

Hormones Secreted by the Stomach

Hormone	Production	Production	Target	Action

	site	stimulus	organ	
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Stomach	Increases secretion by gastric glands; promotes gastric emptying
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Small intestine	Promotes intestinal muscle contraction
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Ileocecal valve	Relaxes valve
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Large intestine	Triggers mass movements
Ghrelin	Stomach mucosa,	Fasting state	Hypothalamus	Regulates food

	mainly fundus	(levels increase just prior to meals)		intake, primarily by stimulating hunger and satiety
Histamine	Stomach mucosa	Presence of food in the stomach	Stomach	Stimulates parietal cells to release HCl
Serotonin	Stomach mucosa	Presence of food in the stomach	Stomach	Contracts stomach muscle
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Stomach	Restricts all gastric secretions, gastric motility, and emptying
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Pancreas	Restricts pancreatic secretions
Somatostatin	Mucosa of	Presence	Small	Reduces

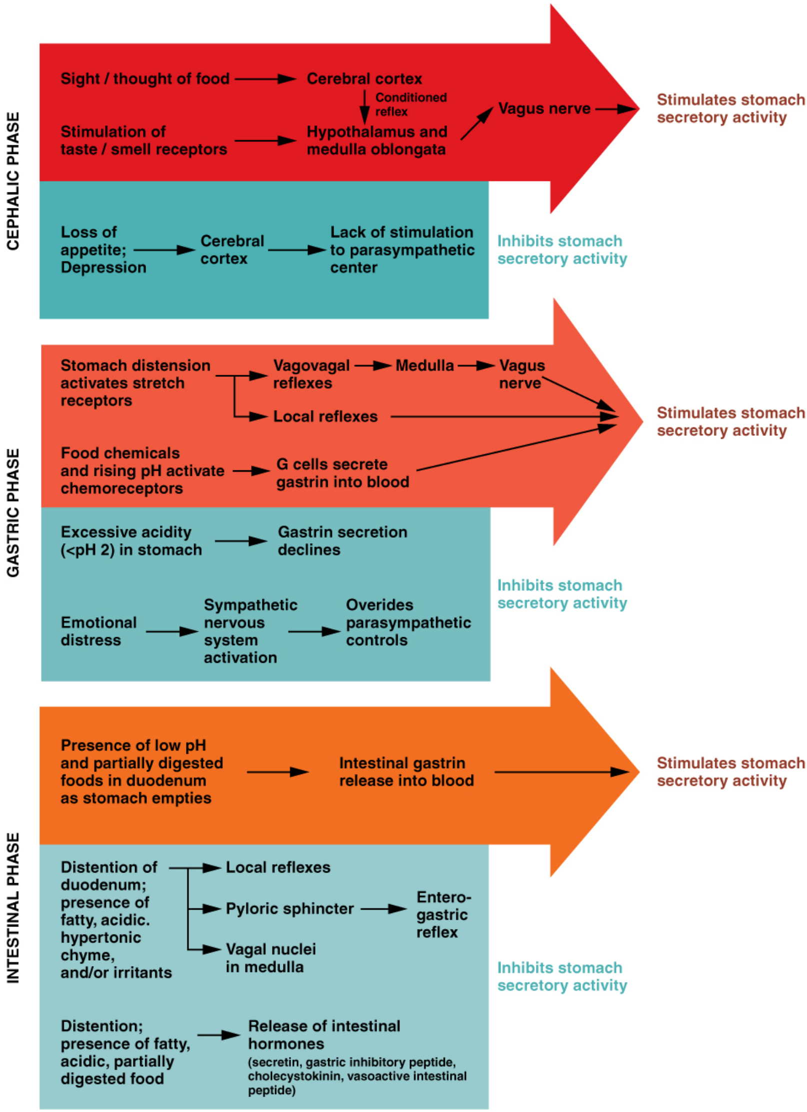
stomach, especially pyloric antrum; also duodenum	of food in the stomach; sympathetic axon stimulation	intestine	intestinal absorption by reducing blood flow

Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases ([link]). However, once gastric secretion begins, all three phases can occur simultaneously.

The Three Phases of Gastric Secretion

Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.



The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or

the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The **intestinal phase** of gastric secretion has both

excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the **mucosal barrier**. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced

every 3 to 6 days.

Homeostatic Imbalances

Ulcers: When the Mucosal Barrier Breaks Down

As effective as the mucosal barrier is, it is not a "fail-safe" mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.

Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.

Antacids help relieve symptoms of ulcers such as "burning" pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.

A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food after enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A **mixing wave** is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called **gastric emptying**, rhythmic mixing

waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12}, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B_{12} injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

Chapter Review

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorbs certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

Interactive Link Questions

Watch this animation that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

Answers may vary.

Review Questions

Which of these cells secrete hormones?

1. parietal cells
2. mucous neck cells
3. enteroendocrine cells
4. chief cells

C

Where does the majority of chemical digestion in the stomach occur?

1. fundus and body
2. cardia and fundus
3. body and pylorus
4. body

A

During gastric emptying, chyme is released into the duodenum through the ______.

1. esophageal hiatus
2. pyloric antrum
3. pyloric canal
4. pyloric sphincter

D

Parietal cells secrete ______.

1. gastrin
2. hydrochloric acid
3. pepsin
4. pepsinogen

B

Critical Thinking Questions

Explain how the stomach is protected from self-digestion and why this is necessary.

The mucosal barrier protects the stomach from self-digestion. It includes a thick coating of bicarbonate-rich mucus; the mucus is physically protective, and bicarbonate neutralizes gastric acid. Epithelial cells meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers, and stem cells quickly replace sloughed off epithelial mucosal cells.

Describe unique anatomical features that enable the stomach to perform digestive functions.

The stomach has an additional inner oblique smooth muscle layer that helps the muscularis churn and mix food. The epithelium includes gastric glands that secrete gastric fluid. The gastric fluid consists mainly of mucous, HCl, and the enzyme pepsin released as pepsinogen.

Glossary

body
: mid-portion of the stomach

cardia
: (also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

cephalic phase
: (also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

chief cell
: gastric gland cell that secretes pepsinogen

enteroendocrine cell
: gastric gland cell that releases hormones

fundus
: dome-shaped region of the stomach above and to the left of the cardia

G cell
: gastrin-secreting enteroendocrine cell

gastric emptying
: process by which mixing waves gradually cause the release of chyme into the duodenum

gastric gland
: gland in the stomach mucosal epithelium that produces gastric juice

gastric phase
: phase of gastric secretion that begins when food enters the stomach

gastric pit
: narrow channel formed by the epithelial lining of the stomach mucosa

gastrin
: peptide hormone that stimulates secretion of hydrochloric acid and gut motility

hydrochloric acid (HCl)
: digestive acid secreted by parietal cells in the stomach

intrinsic factor

glycoprotein required for vitamin B12 absorption in the small intestine

intestinal phase
phase of gastric secretion that begins when chyme enters the intestine

mixing wave
unique type of peristalsis that occurs in the stomach

mucosal barrier
protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell
gastric gland cell that secretes a uniquely acidic mucus

parietal cell
gastric gland cell that secretes hydrochloric acid and intrinsic factor

pepsinogen
inactive form of pepsin

pyloric antrum
wider, more superior part of the pylorus

pyloric canal
narrow, more inferior part of the pylorus

pyloric sphincter

sphincter that controls stomach emptying

pylorus
lower, funnel-shaped part of the stomach that is continuous with the duodenum

ruga
fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

stomach
alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

The Small and Large Intestines

By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning "internal," and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the "guts," they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called "small." In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we'll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m^2, more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum ([link]).

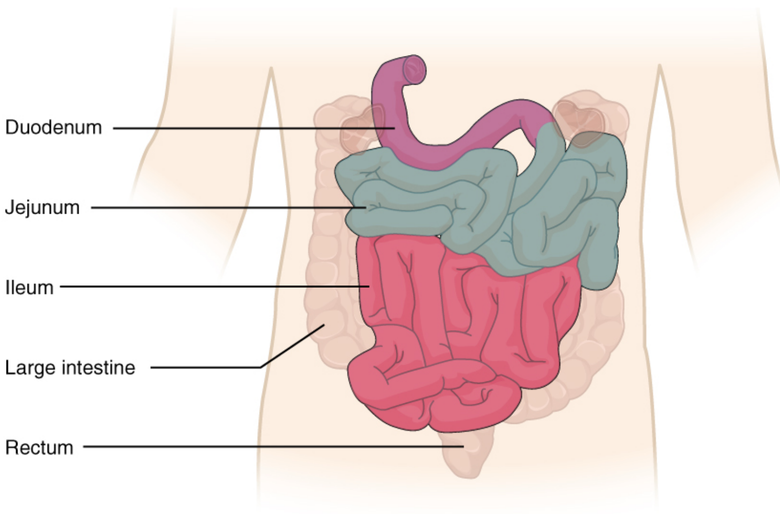
The shortest region is the 25.4-cm (10-in)

duodenum, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the **hepatopancreatic ampulla** (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the **main pancreatic duct** (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the **major duodenal papilla**. The **hepatopancreatic sphincter** (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.

Small Intestine

The three regions of the small intestine are the duodenum, jejunum, and ileum.



The **jejunum** is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means "empty" in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The **ileum** is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the **ileocecal sphincter** (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Parasympathetic nerve fibers from the vagus nerve

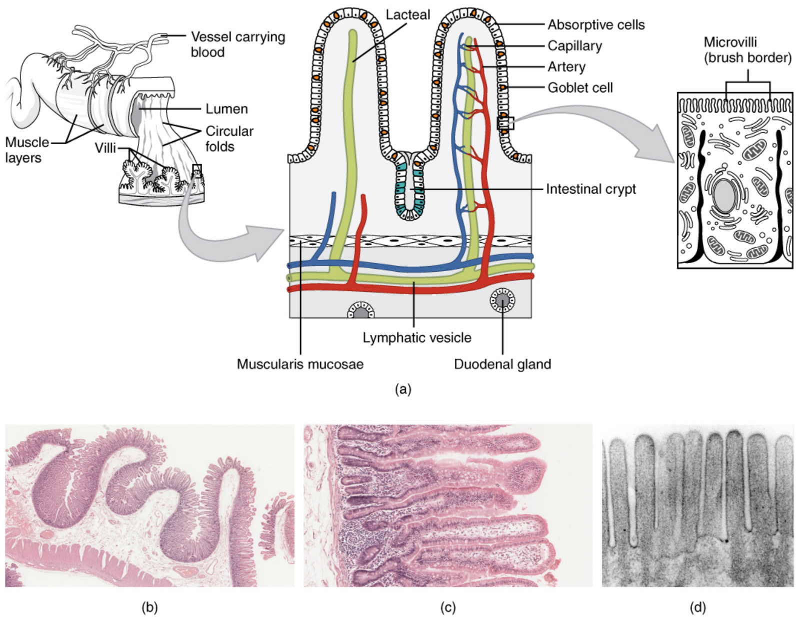
and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli ([link]). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.

Histology of the Small Intestine

(a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Circular folds

Also called a plica circulare, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi**

(singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller (1 μm) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus

greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **intestinal gland** (crypt of Lieberkühn), which is formed by cells that line the crevices (see [link]). These produce **intestinal juice**, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucus-secreting **duodenal glands** (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach.

The roles of the cells in the small intestinal mucosa are detailed in [link].

Cells of the

Small Intestinal Mucosa

Cell type	**Location in the mucosa**	**Function**
Absorptive	Epithelium/ intestinal glands	Digestion and absorption of nutrients in chyme
Goblet	Epithelium/ intestinal glands	Secretion of mucus
Paneth	Intestinal glands	Secretion of the bactericidal enzyme lysozyme; phagocytosis
G cells	Intestinal glands of duodenum	Secretion of the hormone intestinal gastrin
I cells	Intestinal glands of duodenum	Secretion of the hormone cholecystokinin, which stimulates release of pancreatic juices and bile
K cells	Intestinal glands	Secretion of the hormone glucose-dependent insulinotropic peptide, which

		stimulates the release of insulin
M cells	Intestinal glands of duodenum and jejunum	Secretion of the hormone motilin, which accelerates gastric emptying, stimulates intestinal peristalsis, and stimulates the production of pepsin
S cells	Intestinal glands	Secretion of the hormone secretin

Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer's patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer's patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

Watch this animation that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Mechanical Digestion in the Small Intestine

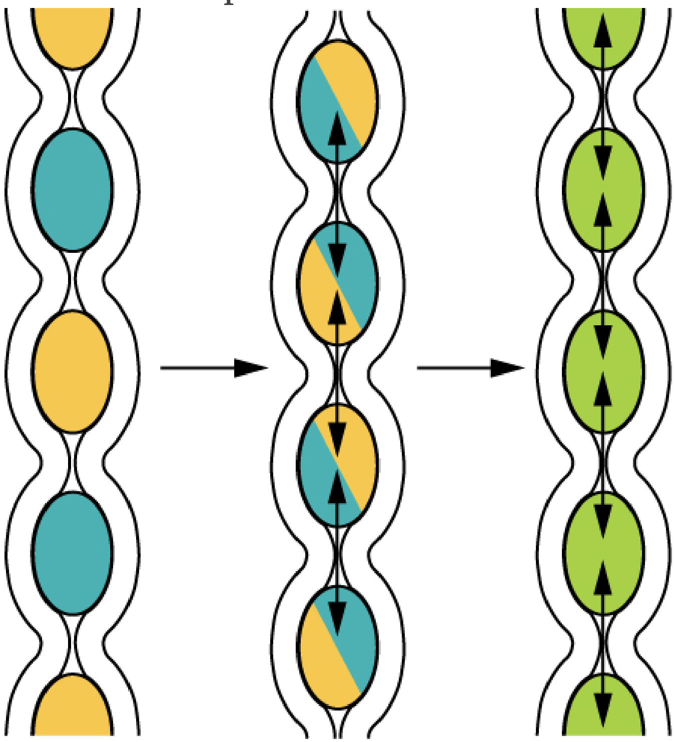
The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly

contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute ([link]).

Segmentation

Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.



When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this

point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes

about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-

threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

Disorders of the…

Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations, most notably Caucasians, are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose

lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

The Large Intestine

The **large intestine** is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small intestine, it is called large because it is more than

twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

Cecum

The first part of the large intestine is the **cecum**, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The **appendix** (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The

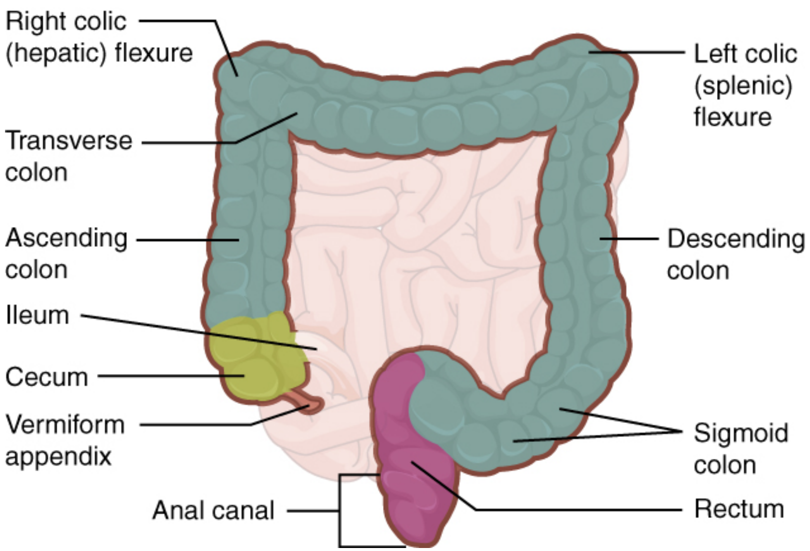
mesoappendix, the mesentery of the appendix, tethers it to the mesentery of the ileum.

Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the **right colic flexure** (hepatic flexure) and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the **left colic flexure** (splenic flexure). From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline ([link]). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Large Intestine

The large intestine includes the cecum, colon, and rectum.



Homeostatic Imbalances

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer. Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most

colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the **rectum** in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

Anal Canal

Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in)

long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The **internal anal sphincter** is made of smooth muscle, and its contractions are involuntary. The **external anal sphincter** is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

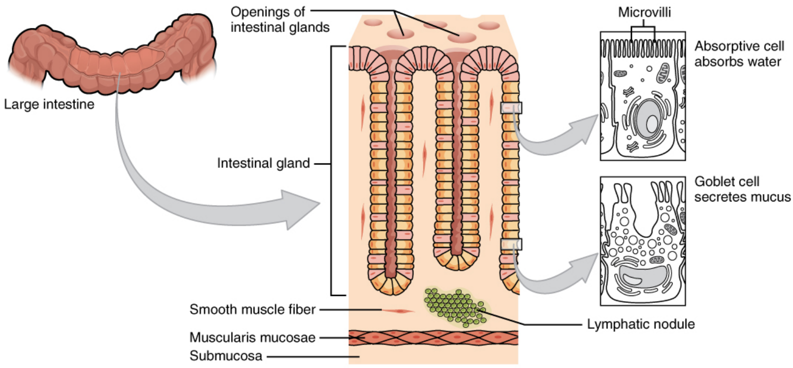
Histology

There are several notable differences between the walls of the large and small intestines ([link]). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more intestinal glands, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

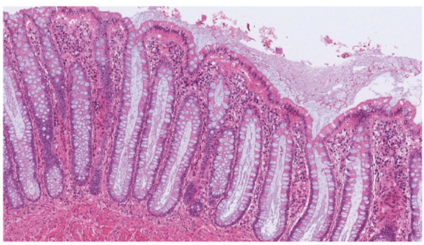
Histology of the large Intestine

(a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet

cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)



(a)



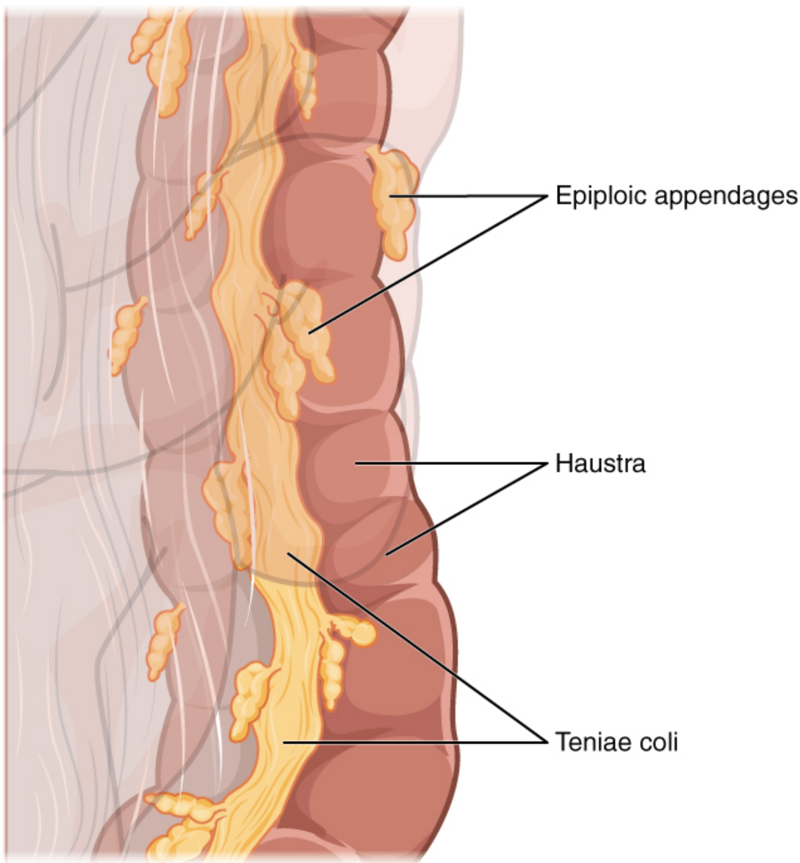
(b)

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages ([link]). The **teniae coli** are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra** (singular = haustrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled

sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

Teniae Coli, Haustra, and Epiploic Appendages



The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of

the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an **anal column**, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an **anal sinus**, secrete mucus that facilitates defecation. The **pectinate line** (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate

chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a

colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving **haustral contraction**. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large

intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a **mass movement**. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the **gastrocolic reflex**, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of **saccharolytic fermentation**, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create **flatus** (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid **feces** (“stool”). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called **Valsalva’s maneuver**, in which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to

the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

By watching this animation you will see that for

the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Chapter Review

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption.

Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

Interactive Link Questions

Watch this animation that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Answers may vary.

By watching this animation, you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Answers may vary.

Review Questions

In which part of the alimentary canal does most digestion occur?

1. stomach
2. proximal small intestine
3. distal small intestine
4. ascending colon

B

Which of these is most associated with villi?

1. haustra
2. lacteals
3. bacterial flora
4. intestinal glands

B

What is the role of the small intestine’s MALT?

1. secreting mucus
2. buffering acidic chyme
3. activating pepsin
4. preventing bacteria from entering the bloodstream

D

Which part of the large intestine attaches to the appendix?

1. cecum
2. ascending colon
3. transverse colon
4. descending colon

A

Critical Thinking Questions

Explain how nutrients absorbed in the small intestine pass into the general circulation.

Nutrients from the breakdown of carbohydrates and proteins are absorbed through a capillary bed in the villi of the small intestine. Lipid breakdown products are absorbed into a lacteal in the villi, and transported via the lymphatic system to the bloodstream.

Why is it important that chyme from the stomach is delivered to the small intestine slowly and in small amounts?

If large quantities of chyme were forced into the small intestine, it would result in osmotic water loss from the blood into the intestinal lumen that could cause potentially life-threatening low blood volume and erosion of the duodenum.

Describe three of the differences between the walls of the large and small intestines.

The mucosa of the small intestine includes circular folds, villi, and microvilli. The wall of the large intestine has a thick mucosal layer, and deeper and more abundant mucus-secreting glands that facilitate the smooth passage of feces. There are three features that are unique to the large intestine: teniae coli, haustra, and epiploic appendages.

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Glossary

anal canal
: final segment of the large intestine

anal column
: long fold of mucosa in the anal canal

anal sinus
: recess between anal columns

appendix
: (vermiform appendix) coiled tube attached to the cecum

ascending colon
: first region of the colon

bacterial flora
: bacteria in the large intestine

brush border
: fuzzy appearance of the small intestinal mucosa created by microvilli

cecum
: pouch forming the beginning of the large intestine

circular fold
: (also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

colon
: part of the large intestine between the cecum and the rectum

descending colon
: part of the colon between the transverse colon and the sigmoid colon

duodenal gland
: (also, Brunner's gland) mucous-secreting gland in the duodenal submucosa

duodenum
: first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

epiploic appendage
: small sac of fat-filled visceral peritoneum attached to teniae coli

external anal sphincter
: voluntary skeletal muscle sphincter in the anal canal

feces
: semisolid waste product of digestion

flatus
: gas in the intestine

gastrocolic reflex
: propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex
: long reflex that increases the strength of segmentation in the ileum

haustrum
: small pouch in the colon created by tonic contractions of teniae coli

haustral contraction
: slow segmentation in the large intestine

hepatopancreatic ampulla
: (also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

hepatopancreatic sphincter
: (also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

ileocecal sphincter
: sphincter located where the small intestine joins with the large intestine

ileum
: end of the small intestine between the jejunum and the large intestine

internal anal sphincter
: involuntary smooth muscle sphincter in the anal canal

intestinal gland
: (also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

intestinal juice
: mixture of water and mucus that helps absorb nutrients from chyme

jejunum
: middle part of the small intestine between the duodenum and the ileum

lacteal
: lymphatic capillary in the villi

large intestine
: terminal portion of the alimentary canal

left colic flexure
: (also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

main pancreatic duct
: (also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

major duodenal papilla
: point at which the hepatopancreatic ampulla

opens into the duodenum

mass movement
: long, slow, peristaltic wave in the large intestine

mesoappendix
: mesentery of the appendix

microvillus
: small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex
: form of peristalsis in the small intestine

motilin
: hormone that initiates migrating motility complexes

pectinate line
: horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

rectal valve
: one of three transverse folds in the rectum where feces is separated from flatus

rectum
: part of the large intestine between the sigmoid colon and anal canal

right colic flexure
: (also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

saccharolytic fermentation
: anaerobic decomposition of carbohydrates

sigmoid colon
: end portion of the colon, which terminates at the rectum

small intestine
: section of the alimentary canal where most digestion and absorption occurs

tenia coli
: one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end

transverse colon
: part of the colon between the ascending colon and the descending colon

Valsalva's maneuver
: voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

villus

projection of the mucosa of the small intestine

Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

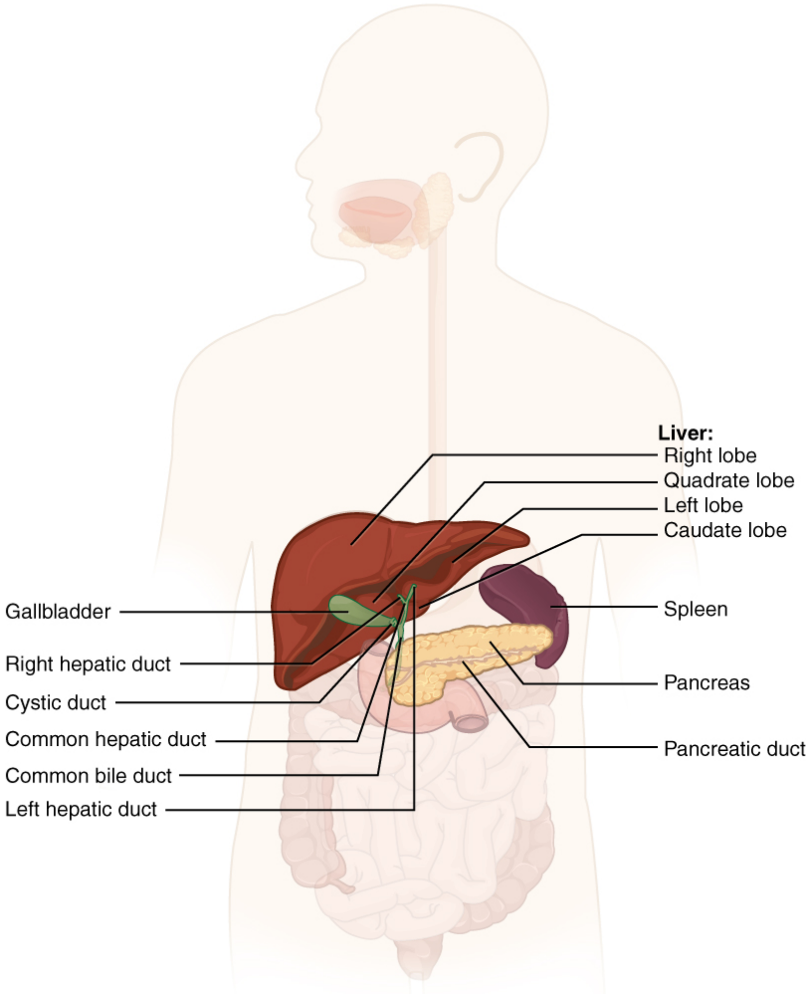
By the end of this section, you will be able to:

- State the main digestive roles of the liver, pancreas, and gallbladder
- Identify three main features of liver histology that are critical to its function
- Discuss the composition and function of bile
- Identify the major types of enzymes and buffers present in pancreatic juice

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder ([link]). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

Accessory Organs

The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.



The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles

in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

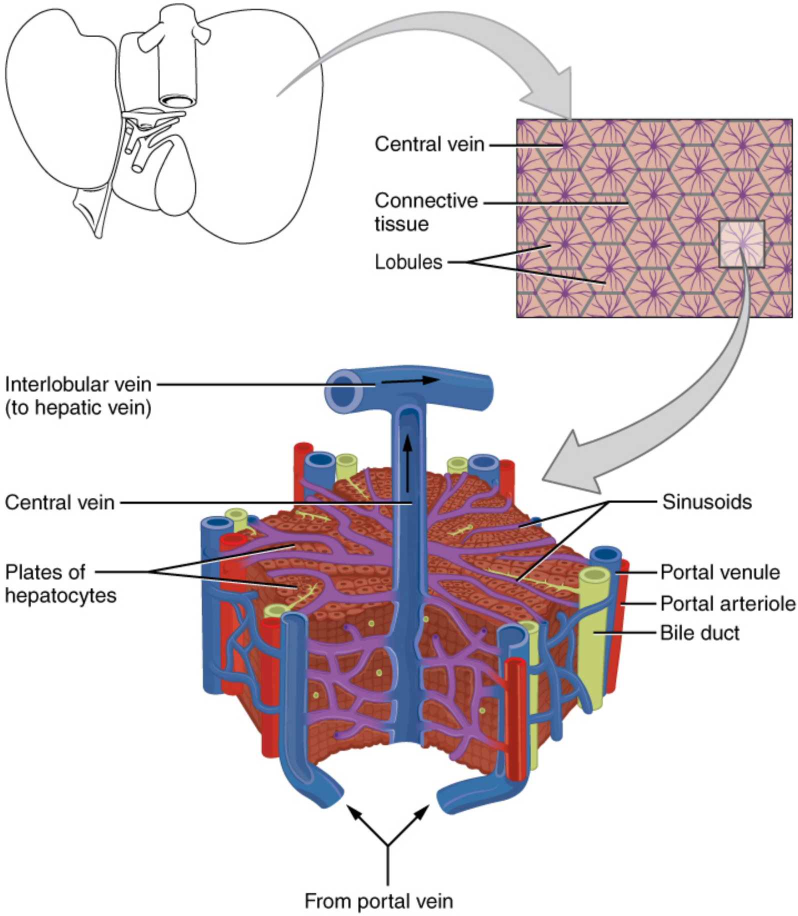
The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The **porta hepatis** ("gate to the liver") is where the **hepatic artery** and **hepatic portal vein** enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in [link], the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In

addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

Microscopic Anatomy of the Liver

The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.



Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A **hepatocyte** is the liver’s main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the portal

vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-

shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme

in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats

are broken down or absorbed.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

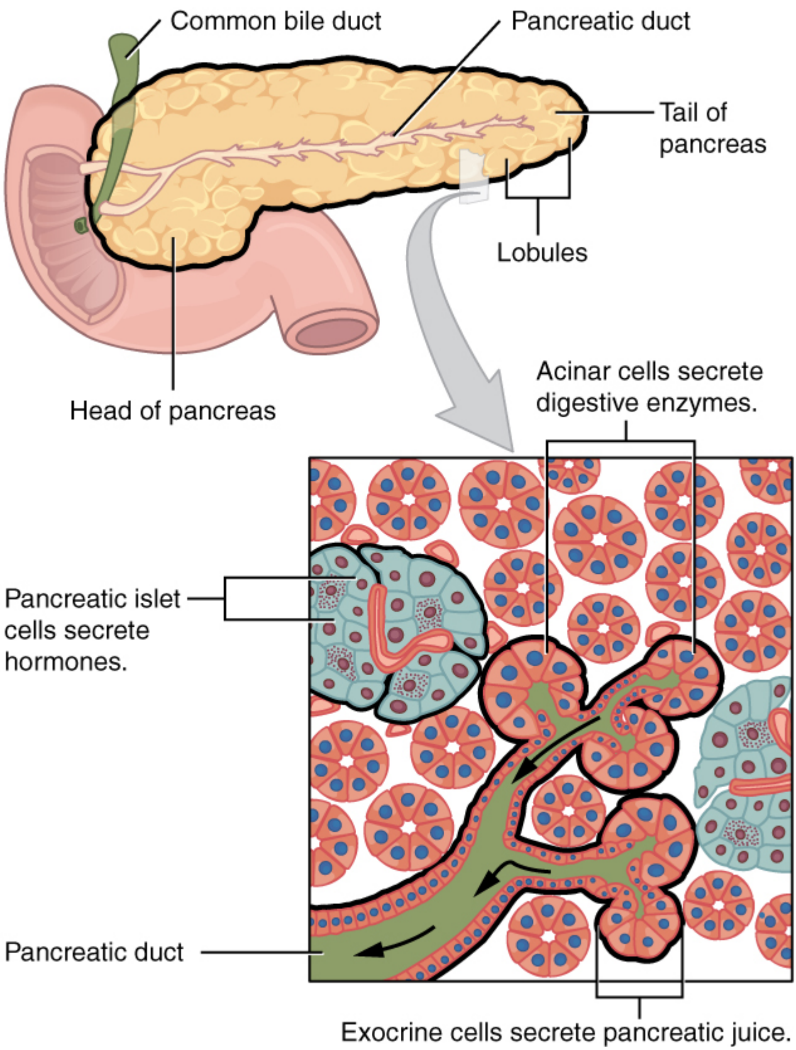
Watch this video to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

The Pancreas

The soft, oblong, glandular **pancreas** lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions ([link]).

Exocrine and Endocrine Pancreas

The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.



The exocrine part of the pancreas arises as little grape-like cell clusters, each called an **acinus** (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich **pancreatic juice** into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver

and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the **accessory duct** (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the

secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

The Gallbladder

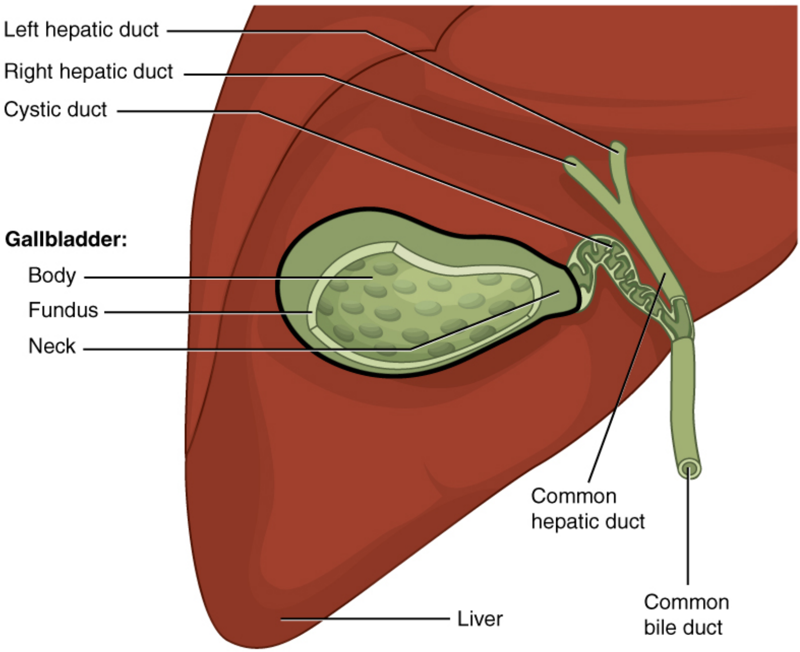
The **gallbladder** is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of

smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the **cystic duct** and into the bile duct ([link]). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

Gallbladder

The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.



Chapter Review

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

Interactive Link Questions

Watch this video to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

Answers may vary.

Review Questions

Which of these statements about bile is true?

1. About 500 mL is secreted daily.
2. Its main function is the denaturation of proteins.
3. It is synthesized in the gallbladder.
4. Bile salts are recycled.

D

Pancreatic juice ______.

1. deactivates bile.
2. is secreted by pancreatic islet cells.
3. buffers chyme.
4. is released into the cystic duct.

C

Critical Thinking Questions

Why does the pancreas secrete some enzymes in their inactive forms, and where are these enzymes activated?

The pancreas secretes protein-digesting enzymes in their inactive forms. If secreted in their active forms, they would self-digest the pancreas. These enzymes are activated in the duodenum.

Describe the location of hepatocytes in the liver and how this arrangement enhances their function.

The hepatocytes are the main cell type of the liver. They process, store, and release nutrients into the blood. Radiating out from the central vein, they are tightly packed around the hepatic sinusoids, allowing the hepatocytes easy access to the blood flowing through the sinusoids.

Glossary

accessory duct

(also, duct of Santorini) duct that runs from the pancreas into the duodenum

acinus
: cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

bile
: alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus
: small duct between hepatocytes that collects bile

bilirubin
: main bile pigment, which is responsible for the brown color of feces

central vein
: vein that receives blood from hepatic sinusoids

common bile duct
: structure formed by the union of the common hepatic duct and the gallbladder’s cystic duct

common hepatic duct
: duct formed by the merger of the two hepatic ducts

cystic duct

duct through which bile drains and enters the gallbladder

enterohepatic circulation
: recycling mechanism that conserves bile salts

enteropeptidase
: intestinal brush-border enzyme that activates trypsinogen to trypsin

gallbladder
: accessory digestive organ that stores and concentrates bile

hepatic artery
: artery that supplies oxygenated blood to the liver

hepatic lobule
: hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein
: vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoid
: blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein

vein that drains into the inferior vena cava

hepatocytes
: major functional cells of the liver

liver
: largest gland in the body whose main digestive function is the production of bile

pancreas
: accessory digestive organ that secretes pancreatic juice

pancreatic juice
: secretion of the pancreas containing digestive enzymes and bicarbonate

porta hepatis
: “gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver

portal triad
: bile duct, hepatic artery branch, and hepatic portal vein branch

reticuloendothelial cell
: (also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

Chemical Digestion and Absorption: A Closer Look

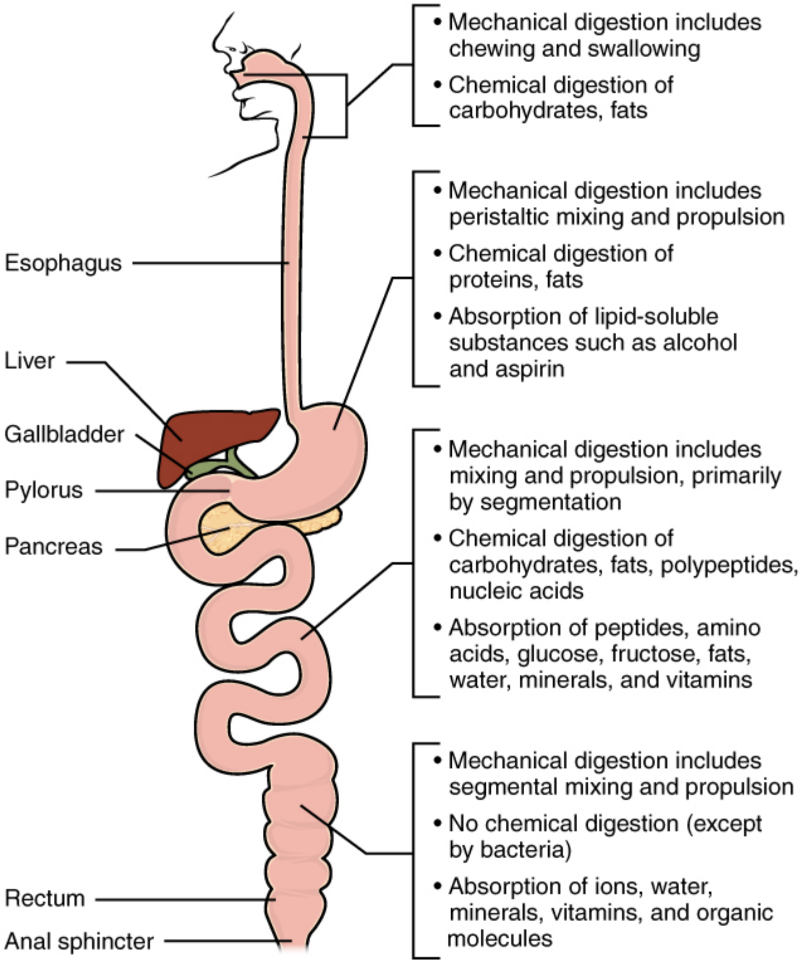
By the end of this section, you will be able to:

- Identify the locations and primary secretions involved in the chemical digestion of carbohydrates, proteins, lipids, and nucleic acids
- Compare and contrast absorption of the hydrophilic and hydrophobic nutrients

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body ([link]). In this section, you will look more closely at the processes of chemical digestion and absorption.

Digestion and Absorption

Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.



Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The

many enzymes involved in chemical digestion are summarized in [link].

The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglycerides
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides
Brush border enzymes	α-Dextrinase	Small intestine	α-Dextrins	Glucose
Brush border enzymes	Enteropeptidase	Small intestine	Trypsinogen	Trypsin

Brush border enzymes	Lactase	Small intestine	Lactose	Glucose and galactose
Brush border enzymes	Maltase	Small intestine	Maltose	Glucose
Brush border enzymes	Nucleosidases and phosphatases	Small intestine	Nucleotides	Phosphates, nitrogenous bases, and pentoses
Brush border enzymes	Peptidases	Small intestine	Aminopeptidase: amino acids at the amino end of peptides Dipeptidase: dipeptides	Aminopeptidase: amino acids and peptides Dipeptidase: amino acids
Brush border enzymes	Sucrase	Small intestine	Sucrose	Glucose and fructose
Pancreatic enzymes	Carboxy-peptidase*	Pancreatic acinar cells	Amino acids at the carboxyl end of peptides	Amino acids and peptides
Pancreatic enzymes	Chymotrypsin*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Elastase*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Nucleases	Pancreatic acinar cells	Ribonuclease: ribonucleic acids Deoxyribonuclease: deoxyribonucleic acids	Nucleotides

Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	α-Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

*These enzymes have been activated by other substances.

Carbohydrate Digestion

The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose

(milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

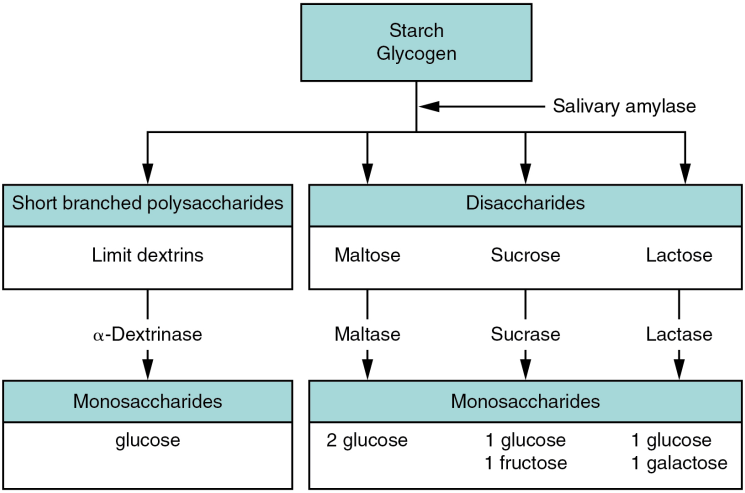
The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the 'heavy lifting' for starch and carbohydrate digestion ([link]). After amylases break down starch into smaller fragments, the brush border enzyme **α-dextrinase** starts working on **α-dextrin**, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

Carbohydrate Digestion Flow Chart

Carbohydrates are broken down into their

monomers in a series of steps.



Protein Digestion

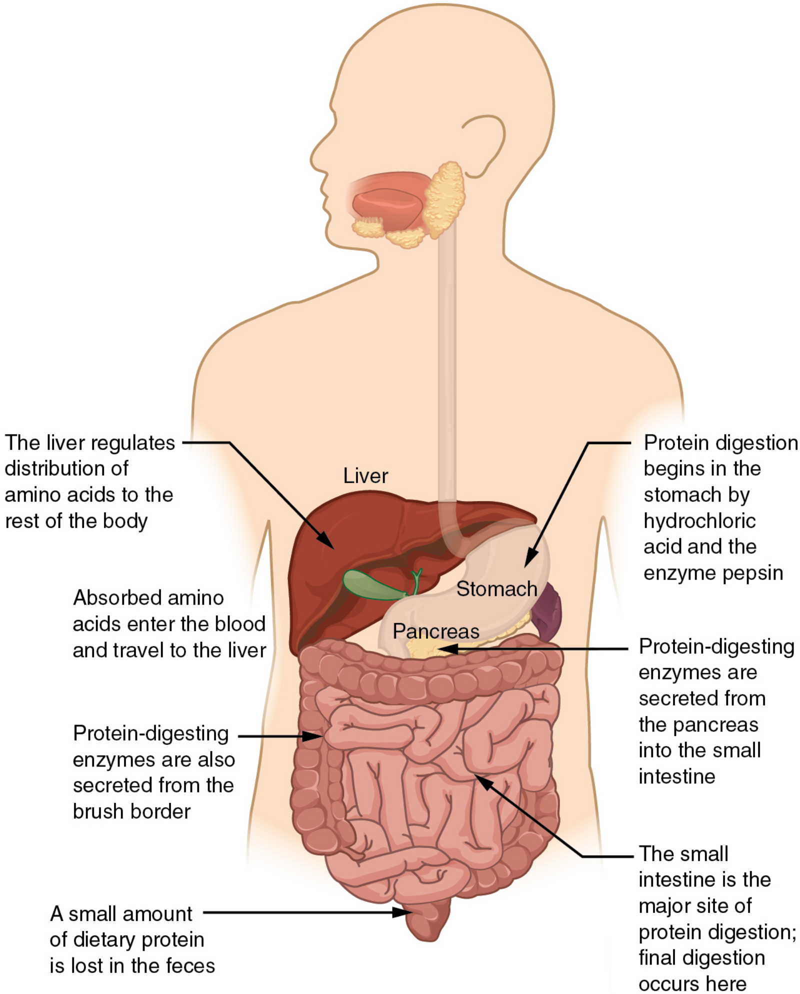
Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine ([link]). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as **aminopeptidase** and **dipeptidase**, which further break down peptide chains. This

results in molecules small enough to enter the bloodstream ([link]).

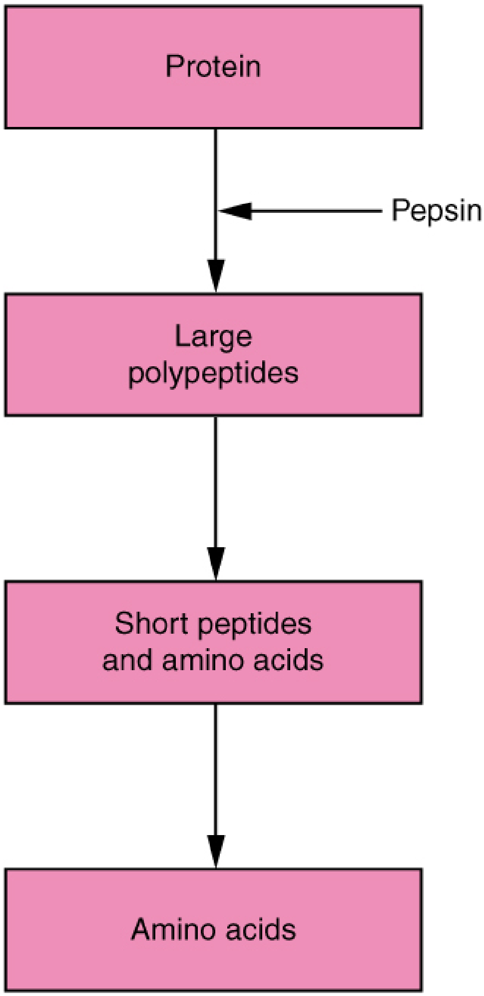
Digestion of Protein

The digestion of protein begins in the stomach and is completed in the small intestine.



Digestion of Protein Flow Chart

Proteins are successively broken down into their amino acid components.



Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

Nucleic Acid Digestion

The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (**nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized [link]

Absorbable Food

Substances Source	Substance
Carbohydrates	Monosaccharides: glucose, galactose, and fructose
Proteins	Single amino acids, dipeptides, and tripeptides
Triglycerides	Monoacylglycerides, glycerol, and free fatty acids
Nucleic acids	Pentose sugars, phosphates, and nitrogenous bases

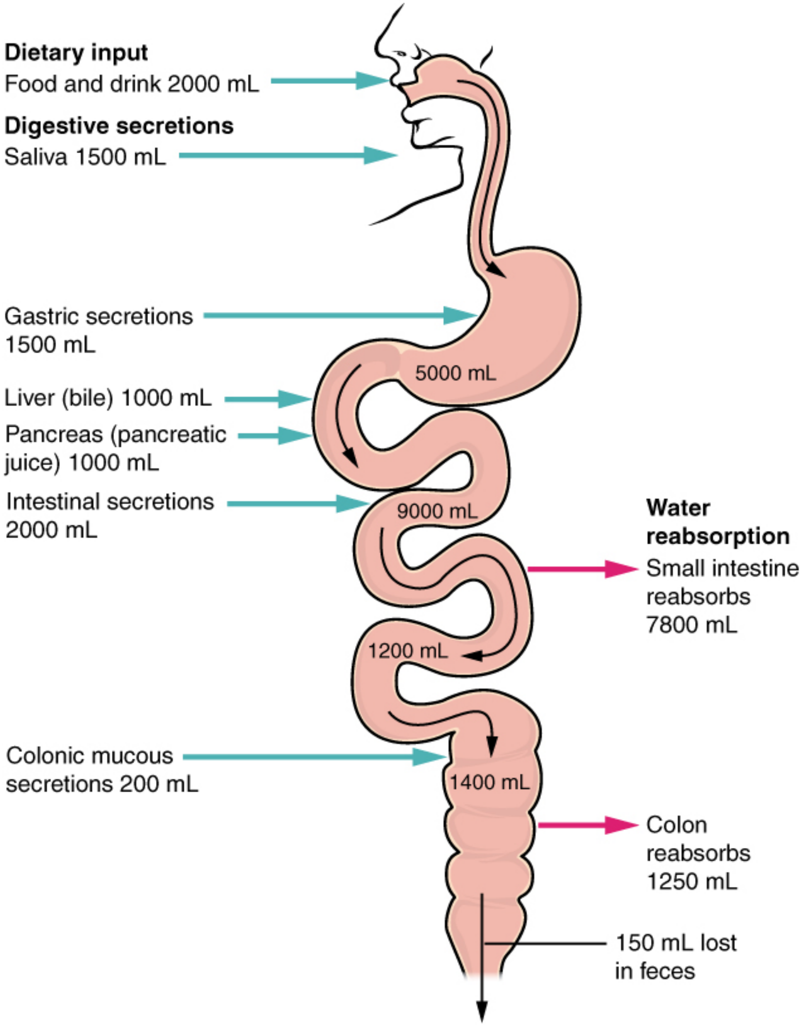
Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Although the entire small intestine is involved in the absorption of water and lipids, most absorption of carbohydrates and

proteins occurs in the jejunum. Notably, bile salts and vitamin B_{12} are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria ([link]).

Digestive Secretions and Absorption of Water

Absorption is a complex process, in which nutrients from digested food are harvested.



Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As you will recall from Chapter 3, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an

area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as "pumps," using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell's plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-

soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in [link].

Absorption in the Alimentary Canal

Food	Breakdown products	Absorption mechanism	Entry to bloodstream	Destination
Carbohydrates	Glucose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein

Carbohydrates	Fructose	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Monoacylglycerides	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct

Lipids	Short-chain fatty acids	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Glycerol	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Nucleic Acids	Nucleic acid digestion products	Active transport via membrane carriers	Capillary blood in villi	Liver via hepatic portal vein

Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides

combine with the transport proteins immediately after the disaccharides are broken down.

Protein Absorption

Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. The small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

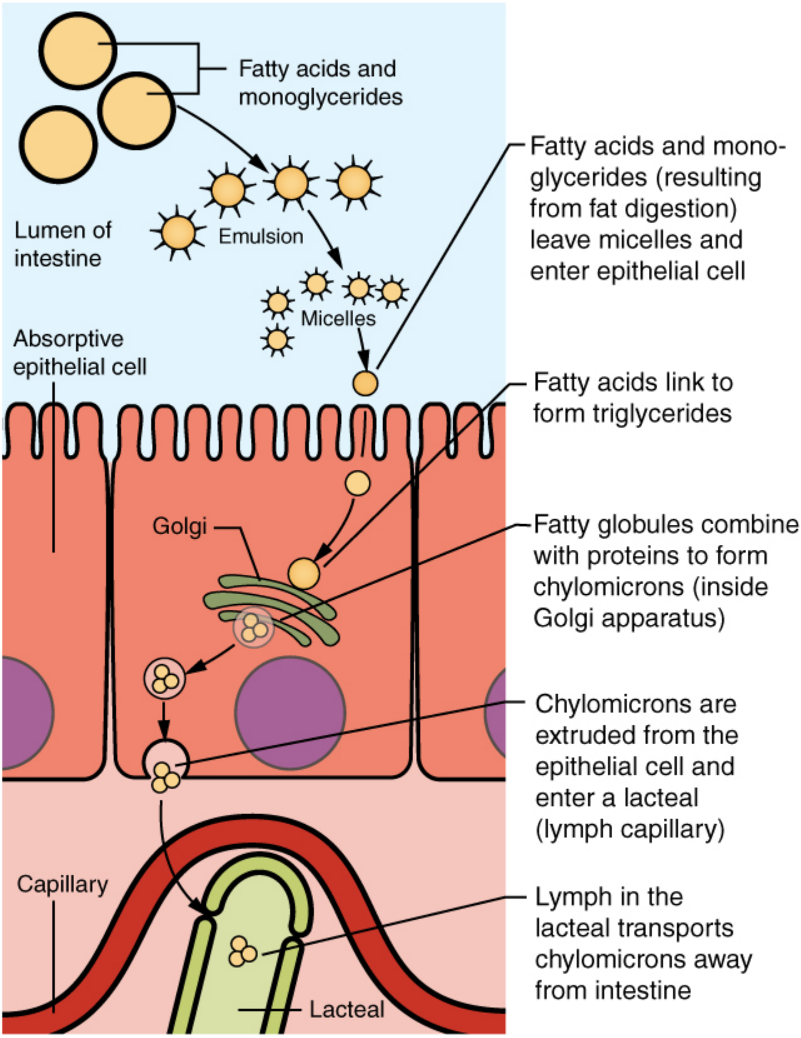
The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a **micelle**, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fat-soluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a **chylomicron**, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell ([link]). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty through the thoracic duct into the subclavian vein of

the circulatory system. Once in the bloodstream, the enzyme **lipoprotein lipase** breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.

Lipid Absorption

Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.



Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated

release of iron into the bloodstream. Since women experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do men.

Calcium—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E, and K) are absorbed along with dietary lipids in micelles via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Most water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by simple diffusion. An exception is vitamin B12, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B12, preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

Chapter Review

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile

salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

Review Questions

Where does the chemical digestion of starch begin?

1. mouth
2. esophagus
3. stomach
4. small intestine

A

Which of these is involved in the chemical digestion of protein?

1. pancreatic amylase

2. trypsin
3. sucrase
4. pancreatic nuclease

B

Where are most fat-digesting enzymes produced?

1. small intestine
2. gallbladder
3. liver
4. pancreas

D

Which of these nutrients is absorbed mainly in the duodenum?

1. glucose
2. iron
3. sodium
4. water

B

Critical Thinking Questions

Explain the role of bile salts and lecithin in the emulsification of lipids (fats).

Bile salts and lecithin can emulsify large lipid globules because they are amphipathic; they have a nonpolar (hydrophobic) region that attaches to the large fat molecules as well as a polar (hydrophilic) region that interacts with the watery chime in the intestine.

How is vitamin B_{12} absorbed?

Intrinsic factor secreted in the stomach binds to the large B_{12} compound, creating a combination that can bind to mucosal receptors in the ileum.

Glossary

α-dextrin
: breakdown product of starch

α-dextrinase
: brush border enzyme that acts on α-dextrins

aminopeptidase

brush border enzyme that acts on proteins

chylomicron
large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

deoxyribonuclease
pancreatic enzyme that digests DNA

dipeptidase
brush border enzyme that acts on proteins

lactase
brush border enzyme that breaks down lactose into glucose and galactose

lipoprotein lipase
enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides

maltase
brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively

micelle
tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core

nucleosidase

brush border enzyme that digests nucleotides

pancreatic amylase
: enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

pancreatic lipase
: enzyme secreted by the pancreas that participates in lipid digestion

pancreatic nuclease
: enzyme secreted by the pancreas that participates in nucleic acid digestion

phosphatase
: brush border enzyme that digests nucleotides

ribonuclease
: pancreatic enzyme that digests RNA

sucrase
: brush border enzyme that breaks down sucrose into glucose and fructose

Introduction
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Metabolism
Metabolism is the sum of all energy-requiring and energy-consuming processes of the body. Many factors contribute to overall metabolism, including lean muscle mass, the amount and quality of food consumed, and the physical demands placed on the human body. (credit: "tableatny"/flickr.com)

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the processes involved in anabolic and catabolic reactions
- List and describe the steps necessary for carbohydrate, lipid, and protein metabolism

- Explain the processes that regulate glucose levels during the absorptive and postabsorptive states
- Explain how metabolism is essential to maintaining body temperature (thermoregulation)
- Summarize the importance of vitamins and minerals in the diet

Eating is essential to life. Many of us look to eating as not only a necessity, but also a pleasure. You may have been told since childhood to start the day with a good breakfast to give you the energy to get through most of the day. You most likely have heard about the importance of a balanced diet, with plenty of fruits and vegetables. But what does this all mean to your body and the physiological processes it carries out each day? You need to absorb a range of nutrients so that your cells have the building blocks for metabolic processes that release the energy for the cells to carry out their daily jobs, to manufacture new proteins, cells, and body parts, and to recycle materials in the cell.

This chapter will take you through some of the chemical reactions essential to life, the sum of which is referred to as metabolism. The focus of these discussions will be anabolic reactions and catabolic reactions. You will examine the various

chemical reactions that are important to sustain life, including why you must have oxygen, how mitochondria transfer energy, and the importance of certain “metabolic” hormones and vitamins.

Metabolism varies, depending on age, gender, activity level, fuel consumption, and lean body mass. Your own metabolic rate fluctuates throughout life. By modifying your diet and exercise regimen, you can increase both lean body mass and metabolic rate. Factors affecting metabolism also play important roles in controlling muscle mass. Aging is known to decrease the metabolic rate by as much as 5 percent per year. Additionally, because men tend have more lean muscle mass then women, their basal metabolic rate (metabolic rate at rest) is higher; therefore, men tend to burn more calories than women do. Lastly, an individual’s inherent metabolic rate is a function of the proteins and enzymes derived from their genetic background. Thus, your genes play a big role in your metabolism. Nonetheless, each person’s body engages in the same overall metabolic processes.

Nutrition and Diet
By the end of this section, you will be able to:

- Explain how different foods can affect metabolism
- Describe a healthy diet, as recommended by the U.S. Department of Agriculture (USDA)
- List reasons why vitamins and minerals are critical to a healthy diet

The carbohydrates, lipids, and proteins in the foods you eat are used for energy to power molecular, cellular, and organ system activities. Importantly, the energy is stored primarily as fats. The quantity and quality of food that is ingested, digested, and absorbed affects the amount of fat that is stored as excess calories. Diet—both what you eat and how much you eat—has a dramatic impact on your health. Eating too much or too little food can lead to serious medical issues, including cardiovascular disease, cancer, anorexia, and diabetes, among others. Combine an unhealthy diet with unhealthy environmental conditions, such as smoking, and the potential medical complications increase significantly.

Food and Metabolism

The amount of energy that is needed or ingested per

day is measured in calories. The nutritional **Calorie** (C) is the amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C. This is different from the calorie (c) used in the physical sciences, which is the amount of heat it takes to raise 1 g of water by 1 °C. When we refer to "calorie," we are referring to the nutritional Calorie.

On average, a person needs 1500 to 2000 calories per day to sustain (or carry out) daily activities. The total number of calories needed by one person is dependent on their body mass, age, height, gender, activity level, and the amount of exercise per day. If exercise is regular part of one’s day, more calories are required. As a rule, people underestimate the number of calories ingested and overestimate the amount they burn through exercise. This can lead to ingestion of too many calories per day. The accumulation of an extra 3500 calories adds one pound of weight. If an excess of 200 calories per day is ingested, one extra pound of body weight will be gained every 18 days. At that rate, an extra 20 pounds can be gained over the course of a year. Of course, this increase in calories could be offset by increased exercise. Running or jogging one mile burns almost 100 calories.

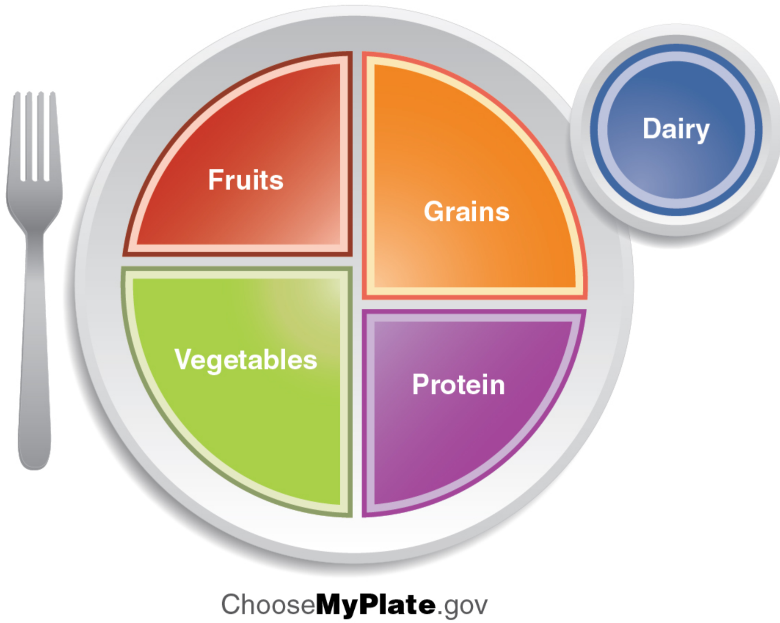
The type of food ingested also affects the body’s metabolic rate. Processing of carbohydrates requires less energy than processing of proteins. In fact, the breakdown of carbohydrates requires the least

amount of energy, whereas the processing of proteins demands the most energy. In general, the amount of calories ingested and the amount of calories burned determines the overall weight. To lose weight, the number of calories burned per day must exceed the number ingested. Calories are in almost everything you ingest, so when considering calorie intake, beverages must also be considered.

To help provide guidelines regarding the types and quantities of food that should be eaten every day, the USDA has updated their food guidelines from MyPyramid to MyPlate. They have put the recommended elements of a healthy meal into the context of a place setting of food. MyPlate categorizes food into the standard six food groups: fruits, vegetables, grains, protein foods, dairy, and oils. The accompanying website gives clear recommendations regarding quantity and type of each food that you should consume each day, as well as identifying which foods belong in each category. The accompanying graphic ([link]) gives a clear visual with general recommendations for a healthy and balanced meal. The guidelines recommend to "Make half your plate fruits and vegetables." The other half is grains and protein, with a slightly higher quantity of grains than protein. Dairy products are represented by a drink, but the quantity can be applied to other dairy products as well.

MyPlate

The U.S. Department of Agriculture developed food guidelines called MyPlate to help demonstrate how to maintain a healthy lifestyle.



ChooseMyPlate.gov provides extensive online resources for planning a healthy diet and lifestyle, including offering weight management tips and recommendations for physical activity. It also includes the SuperTracker, a web-based application to help you analyze your own diet and physical activity.

Everyday Connections

Metabolism and Obesity

Obesity in the United States is epidemic. The rate

of obesity has been steadily rising since the 1980s. In the 1990s, most states reported that less than 10 percent of their populations was obese, and the state with the highest rate reported that only 15 percent of their population was considered obese. By 2010, the U.S. Centers for Disease Control and Prevention reported that nearly 36 percent of adults over 20 years old were obese and an additional 33 percent were overweight, leaving only about 30 percent of the population at a healthy weight. These studies find the highest levels of obesity are concentrated in the southern states. They also find the level of childhood obesity is rising.

Obesity is defined by the **body mass index (BMI)**, which is a measure of an individual’s weight-to-height ratio. The normal, or healthy, BMI range is between 18 and 24.9 kg/m^2. Overweight is defined as a BMI of 25 to 29.9 kg/m^2, and obesity is considered to be a BMI greater than 30 kg/m^2.

Obesity can arise from a number of factors, including overeating, poor diet, sedentary lifestyle, limited sleep, genetic factors, and even diseases or drugs. Severe obesity (morbid obesity) or long-term obesity can result in serious medical conditions, including coronary heart disease; type 2 diabetes; endometrial, breast, or colon cancer; hypertension (high blood pressure); dyslipidemia (high cholesterol or elevated triglycerides); stroke; liver disease; gall bladder disease; sleep apnea or respiratory diseases; osteoarthritis; and infertility.

Research has shown that losing weight can help reduce or reverse the complications associated with these conditions.

Vitamins

Vitamins are organic compounds found in foods and are a necessary part of the biochemical reactions in the body. They are involved in a number of processes, including mineral and bone metabolism, and cell and tissue growth, and they act as cofactors for energy metabolism. The B vitamins play the largest role of any vitamins in metabolism ([link] and [link]).

You get most of your vitamins through your diet, although some can be formed from the precursors absorbed during digestion. For example, the body synthesizes vitamin A from the β-carotene in orange vegetables like carrots and sweet potatoes. Vitamins are either fat-soluble or water-soluble. Fat-soluble vitamins A, D, E, and K, are absorbed through the intestinal tract with lipids in chylomicrons. Vitamin D is also synthesized in the skin through exposure to sunlight. Because they are carried in lipids, fat-soluble vitamins can accumulate in the lipids stored in the body. If excess vitamins are retained in the

lipid stores in the body, hypervitaminosis can result.

Water-soluble vitamins, including the eight B vitamins and vitamin C, are absorbed with water in the gastrointestinal tract. These vitamins move easily through bodily fluids, which are water based, so they are not stored in the body. Excess water-soluble vitamins are excreted in the urine. Therefore, hypervitaminosis of water-soluble vitamins rarely occurs, except with an excess of vitamin supplements.

Fat-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
A retinal or β-carotene	Yellow and orange fruits and vegetables, dark green leafy	700–900 μg	Eye and bone development, immune function	Night blindness, epithelial changes, immune system deficiency

	vegetables, eggs, milk, liver			
D cholecalciferol	Dairy products, egg yolks; also synthesized in the skin from exposure to sunlight	5–15 μg	Aids in calcium absorption, promoting bone growth	Rickets, bone pain, muscle weakness, increased risk of death from cardiovascular disease, cognitive impairment, asthma in children, cancer
E tocopherols	Seeds, nuts, vegetable oils, avocados, wheat germ	15 mg	Antioxidant	Anemia
K phylloquinone	Dark green leafy vegetables, broccoli, Brussels	90–120 ug	Blood clotting, bone health	Hemorrhagic disease of newborn in infants; uncommon in adults

sprouts, cabbage

Water-soluble Vitamins				
Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B1 thiamine	Whole grains, enriched bread and cereals, milk, meat	1.1–1.2 mg	Carbohydrate metabolism	Beriberi, Wernicke-Korsikoff syndrome
B2 riboflavin	Brewer’s yeast, almonds, milk, organ meats, legumes, enriched breads and	1.1–1.3 mg	Synthesis of FAD for metabolism, production of red blood cells	Fatigue, slowed growth, digestive problems, light sensitivity, epithelial problems like cracks

	cereals, broccoli, asparagus			in the corners of the mouth
B3 niacin	Meat, fish, poultry, enriched breads and cereals, peanuts	14–16 mg	Synthesis of NAD, nerve function, cholesterol production	Cracked, scaly skin; dementia; diarrhea; also known as pellagra
B5 pantothenic acid	Meat, poultry, potatoes, oats, enriched breads and cereals, tomatoes	5 mg	Synthesis of coenzyme A in fatty acid metabolism	Rare: symptoms may include fatigue, insomnia, depression, irritability
B6 pyridoxine	Potatoes, bananas, beans, seeds, nuts, meat, poultry, fish, eggs, dark green leafy vegetables,	1.3–1.5 mg	Sodium and potassium balance, red blood cell synthesis, protein metabolism	Confusion, irritability, depression, mouth and tongue sores

	soy, organ meats			
B7 biotin	Liver, fruits, meats	30 μg	Cell growth, metabolism of fatty acids, production of blood cells	Rare in developed countries; symptoms include dermatitis, hair loss, loss of muscular coordination
B9 folic acid	Liver, legumes, dark green leafy vegetables, enriched breads and cereals, citrus fruits	400 μg	DNA/ protein synthesis	Poor growth, gingivitis, appetite loss, shortness of breath, gastrointestinal problems, mental deficits
B12 cyanocobalamin	Fish, meat, poultry, dairy products, eggs	2.4 μg	Fatty acid oxidation, nerve cell function, red blood cell production	Pernicious anemia, leading to nerve cell damage

C ascorbic acid	Citrus fruits, red berries, peppers, tomatoes, broccoli, dark green leafy vegetables	75–90 mg	Necessary to produce collagen for formation of connective tissue and teeth, and for wound healing	Dry hair, gingivitis, bleeding gums, dry and scaly skin, slow wound healing, easy bruising, compromised immunity; can lead to scurvy

Minerals

Minerals in food are inorganic compounds that work with other nutrients to ensure the body functions properly. Minerals cannot be made in the body; they come from the diet. The amount of minerals in the body is small—only 4 percent of the total body mass—and most of that consists of the minerals that the body requires in moderate quantities: potassium, sodium, calcium, phosphorus, magnesium, and chloride.

The most common minerals in the body are calcium and phosphorous, both of which are stored in the

skeleton and necessary for the hardening of bones. Most minerals are ionized, and their ionic forms are used in physiological processes throughout the body. Sodium and chloride ions are electrolytes in the blood and extracellular tissues, and iron ions are critical to the formation of hemoglobin. There are additional trace minerals that are still important to the body's functions, but their required quantities are much lower.

Like vitamins, minerals can be consumed in toxic quantities (although it is rare). A healthy diet includes most of the minerals your body requires, so supplements and processed foods can add potentially toxic levels of minerals. [link] and [link] provide a summary of minerals and their function in the body.

Major Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Potassium	Meats, some fish, fruits,	4700 mg	Nerve and muscle function;	Hypokalemia: weakness, fatigue,

	vegetables, legumes, dairy products		acts as an electrolyte	muscle cramping, gastrointestinal problems, cardiac problems
Sodium	Table salt, milk, beets, celery, processed foods	2300 mg	Blood pressure, blood volume, muscle and nerve function	Rare
Calcium	Dairy products, dark green leafy vegetables, blackstrap molasses, nuts, brewer's yeast, some fish	1000 mg	Bone structure and health; nerve and muscle functions, especially cardiac function	Slow growth, weak and brittle bones
Phosphorous	Meat, milk	700 mg	Bone formation, metabolism, ATP production	Rare
Magnesium	Whole	310–420	Enzyme	Agitation,

	grains, nuts, leafy green vegetables	mg	activation, production of energy, regulation of other nutrients	anxiety, sleep problems, nausea and vomiting, abnormal heart rhythms, low blood pressure, muscular problems
Chloride	Most foods, salt, vegetables, especially seaweed, tomatoes, lettuce, celery, olives	2300 mg	Balance of body fluids, digestion	Loss of appetite, muscle cramps

Trace Minerals

Mineral	Sources	Recommended	Function	Problems

		daily allowance		associated with deficiency
Iron	Meat, poultry, fish, shellfish, legumes, nuts, seeds, whole grains, dark leafy green vegetables	8–18 mg	Transport of oxygen in blood, production of ATP	Anemia, weakness, fatigue
Zinc	Meat, fish, poultry, cheese, shellfish	8–11 mg	Immunity, reproduction, growth, blood clotting, insulin and thyroid function	Loss of appetite, poor growth, weight loss, skin problems, hair loss, vision problems, lack of taste or smell
Copper	Seafood, organ meats,	900 μg	Red blood cell production,	Anemia, low body temperature,

	nuts, legumes, chocolate, enriched breads and cereals, some fruits and vegetables		nerve and immune system function, collagen formation, acts as an antioxidant	bone fractures, low white blood cell concentration, irregular heartbeat, thyroid problems
Iodine	Fish, shellfish, garlic, lima beans, sesame seeds, soybeans, dark leafy green vegetables	150 μg	Thyroid function	Hypothyroidism: fatigue, weight gain, dry skin, temperature sensitivity
Sulfur	Eggs, meat, poultry, fish, legumes	None	Component of amino acids	Protein deficiency
Fluoride	Fluoridated water	3–4 mg	Maintenance of bone and tooth structure	Increased cavities, weak bones and teeth

Manganese	Nuts, seeds, whole grains, legumes	1.8–2.3 mg	Formation of connective tissue and bones, blood clotting, sex hormone development, metabolism, brain and nerve function	Infertility, bone malformation, weakness, seizures
Cobalt	Fish, nuts, leafy green vegetables, whole grains	None	Component of B12	None
Selenium	Brewer's yeast, wheat germ, liver, butter, fish, shellfish, whole grains	55 μg	Antioxidant, thyroid function, immune system function	Muscle pain
Chromium	Whole	25–35 μg	Insulin	High

	grains, lean meats, cheese, black pepper, thyme, brewer's yeast		function	blood sugar, triglyceride, and cholesterol levels
Molybdenum	Legumes, whole grains, nuts	45 μg	Cofactor for enzymes	Rare

Chapter Review

Nutrition and diet affect your metabolism. More energy is required to break down fats and proteins than carbohydrates; however, all excess calories that are ingested will be stored as fat in the body. On average, a person requires 1500 to 2000 calories for normal daily activity, although routine exercise will increase that amount. If you ingest more than that, the remainder is stored for later use. Conversely, if you ingest less than that, the energy stores in your body will be depleted. Both the quantity and quality of the food you eat affect your metabolism and can affect your overall health. Eating too much or too little can result in serious medical conditions,

including cardiovascular disease, cancer, and diabetes.

Vitamins and minerals are essential parts of the diet. They are needed for the proper function of metabolic pathways in the body. Vitamins are not stored in the body, so they must be obtained from the diet or synthesized from precursors available in the diet. Minerals are also obtained from the diet, but they are also stored, primarily in skeletal tissues.

Review Questions

A deficiency in vitamin A can result in _____.

1. improper bone development
2. scurvy
3. improper eye development or sight
4. all of the above

C

Rickets results in improper bone development in children that arises from the malabsorption of calcium and a deficiency in _____.

1. vitamin D

2. vitamin C
3. vitamin B12
4. niacin

A

Consuming which type of food will help the most with weight loss?

1. fats
2. vegetables
3. lean meats
4. fruits

C

Which of the following is stored in the body?

1. thiamine
2. phosphorous
3. folic acid
4. vitamin C

B

Critical Thinking Questions

Weight loss and weight gain are complex processes. What are some of the main factors that influence weight gain in people?

Factors that influence weight gain are food intake (both quantity and quality), environmental factors, height, exercise level, some drugs or disease states, and genes.

Some low-fat or non-fat foods contain a large amount of sugar to replace the fat content of the food. Discuss how this leads to increased fat in the body (and weight gain) even though the item is non-fat.

Although these foods technically do not have fat added, many times a significant amount of sugar is added to sweeten the food and make it taste better. These foods are non-fat; however, they can lead to significant fat storage or weight gain because the excess sugar is broken down into pyruvate, but overloads the Krebs cycle. When this happens, the sugar is converted into fat through lipogenesis and stored in adipose tissues.

Glossary

body mass index (BMI)
: relative amount of body weight compared to the overall height; a BMI ranging from 18–24.9 is considered normal weight, 25–29.9 is considered overweight, and greater than 30 is considered obese

calorie
: amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C

minerals
: inorganic compounds required by the body to ensure proper function of the body

vitamins
: organic compounds required by the body to perform biochemical reactions like metabolism and bone, cell, and tissue growth

Introduction
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Sewage Treatment Plant
(credit: “eutrophication&hypoxia”/flickr.com)

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the composition of urine
- Label structures of the urinary system
- Characterize the roles of each of the parts of the urinary system
- Illustrate the macroscopic and microscopic structures of the kidney
- Trace the flow of blood through the kidney
- Outline how blood is filtered in the kidney

nephron

- Provide symptoms of kidney failure
- List some of the solutes filtered, secreted, and reabsorbed in different parts of the nephron
- Describe the role of a portal system in the kidney
- Explain how urine osmolarity is hormonally regulated
- Describe the regulation of major ions by the kidney
- Summarize the role of the kidneys in maintaining acid–base balance

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to

calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: “What happens if this does not work?” This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one’s life.

Watch this video from the Howard Hughes Medical Institute for an introduction to the urinary system.

Physical Characteristics of Urine

By the end of this section, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors ([link]). Some of the characteristics such as color and odor are rough descriptors of your

state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Normal Urine Characteristics

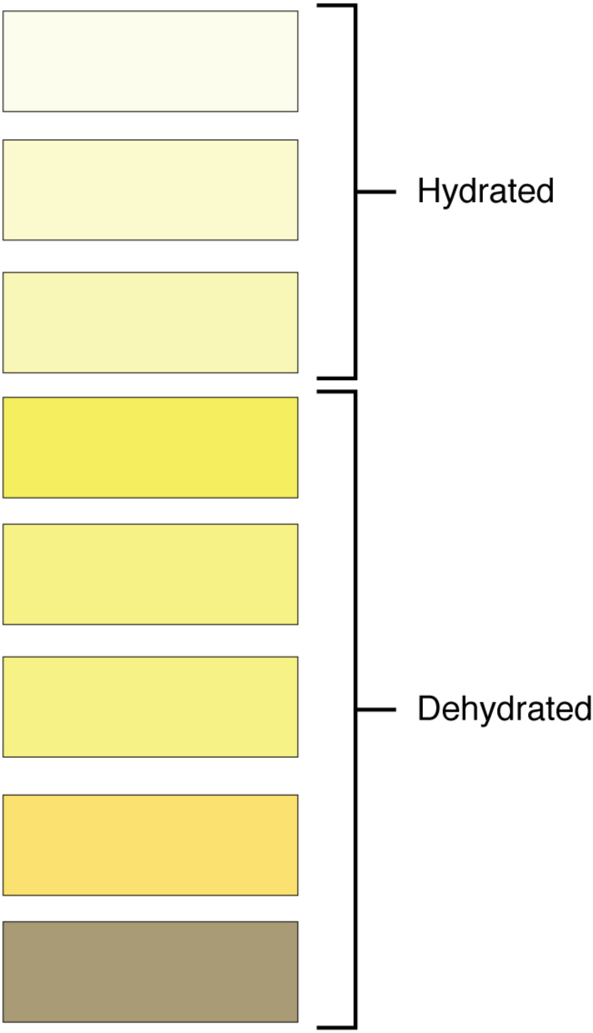
Characteristic	Normal values
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032
Osmolarity	40–1350 mOsmol/kg
Urobilinogen	0.2–1.0 mg/100 mL
White blood cells	0–2 HPF (per high-power field of microscope)

Leukocyte esterase	None
Protein	None or trace
Bilirubin	< 0.3 mg/100 mL
Ketones	None
Nitrites	None
Blood	None
Glucose	None

Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction ([link]). The "heme" of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark "tea" or "cola" hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so

ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Urine Color



Urine volume varies considerably. The normal range is one to two liters per day ([link]). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**.

Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Urine Volumes

Volume condition	Volume	Causes
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as

		diuretics; sickle cell anemia; excessive water intake
Oliguria	300–500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	< 50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence

of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than **specific gravity**. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H_2O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. **Leukocyte esterase** is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the

bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

Chapter Review

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient

intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

Review Questions

Diabetes insipidus or diabetes mellitus would most likely be indicated by ______.

1. anuria
2. polyuria
3. oliguria
4. none of the above

B

The color of urine is determined mainly by ______.

1. diet
2. filtration rate

3. byproducts of red blood cell breakdown
4. filtration efficiency

C

Production of less than 50 mL/day of urine is called ______.

1. normal
2. polyuria
3. oliguria
4. anuria

D

Critical Thinking Questions

What is suggested by the presence of white blood cells found in the urine?

The presence of white blood cells found in the urine suggests urinary tract infection.

Both diabetes mellitus and diabetes insipidus

produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?

Diabetes mellitus would result in urine containing glucose, and diabetes insipidus would produce urine with very low osmolarity (low specific gravity, dilute).

Glossary

anuria
: absence of urine produced; production of 50 mL or less per day

leukocyte esterase
: enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

oliguria
: below normal urine production of 400–500 mL/day

polyuria
: urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

specific gravity

weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

urinalysis
: analysis of urine to diagnose disease

urochrome
: heme-derived pigment that imparts the typical yellow color of urine

Gross Anatomy of the Kidney

By the end of this section, you will be able to:

- Describe the external structure of the kidney, including its location, support structures, and covering
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast the cortical and juxtamedullary nephrons
- Name structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this video to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is “printed.” The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

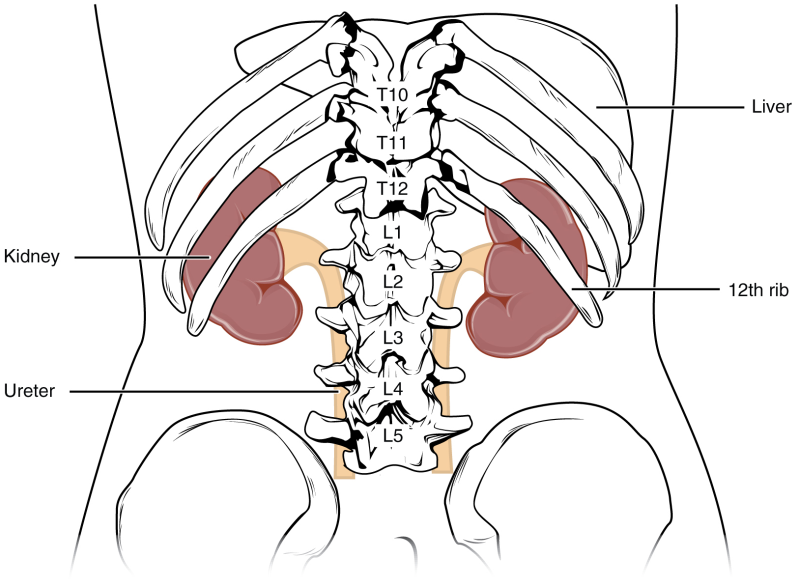
External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs ([link]). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule

composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the **renal fat pad**, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

Kidneys

The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

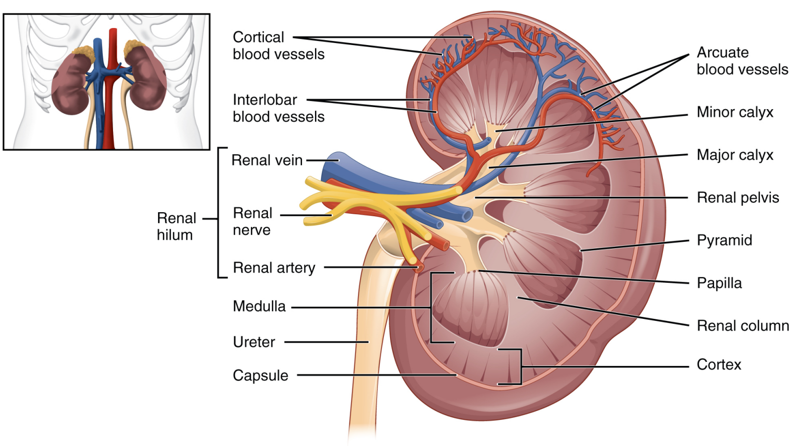


On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** ([link]). The **renal columns** are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

Left Kidney



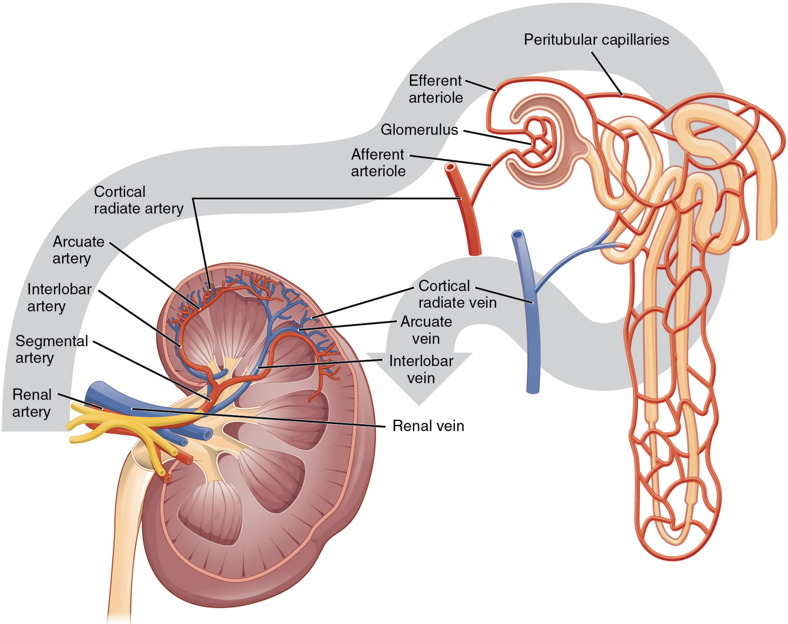
Renal Hilum

The **renal hilum** is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyxes in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex ([link]). The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

Blood Flow in the Kidney

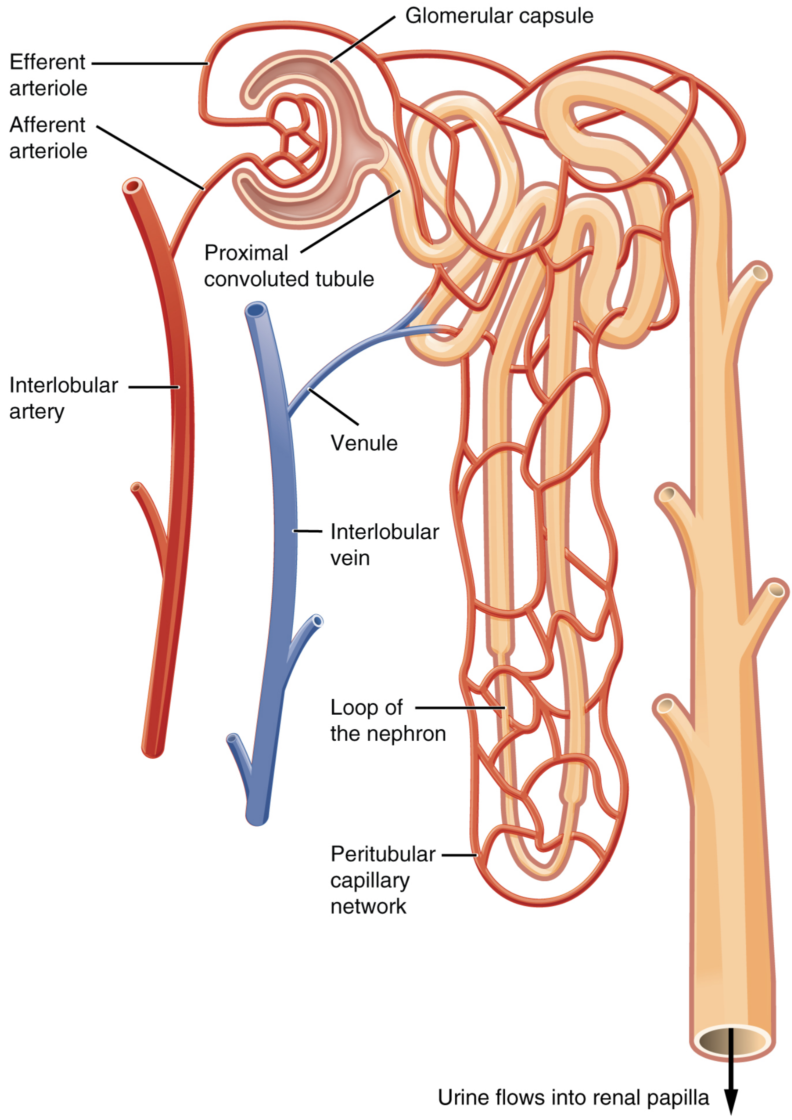


Nephrons are the "functional units" of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the **glomerulus**. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is **Bowman's capsule**. The glomerulus and Bowman's capsule together form the **renal corpuscle**. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole** ([link]). These will next form a capillary network around the more distal portions of the nephron tubule, the **peritubular capillaries**

and **vasa recta**, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)

Blood Flow in the Nephron

The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.


Glomerular capsule
Efferent arteriole
Afferent arteriole
Proximal convoluted tubule
Interlobular artery
Venule
Interlobular vein
Loop of the nephron
Peritubular capillary network
Urine flows into renal papilla

Visit this link to view an interactive tutorial of the flow of blood through the kidney.

Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

Chapter Review

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two

kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the "functional units." A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman's capsule. A portal system is formed when the blood flows through a second capillary bed surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which merge to form major calyces; the filtrate then proceeds to the renal pelvis and finally the ureters.

Review Questions

The renal pyramids are separated from each other by extensions of the renal cortex called ______.

1. renal medulla

2. minor calyces
3. medullary cortices
4. renal columns

D

The primary structure found within the medulla is the ______.

1. loop of Henle
2. minor calyces
3. portal system
4. ureter

A

The right kidney is slightly lower because ______.

1. it is displaced by the liver
2. it is displace by the heart
3. it is slightly smaller
4. it needs protection of the lower ribs

A

Critical Thinking Questions

What anatomical structures provide protection to the kidney?

Retroperitoneal anchoring, renal fat pads, and ribs provide protection to the kidney.

How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?

The renal portal system has an artery between the first and second capillary bed. The others have a vein.

Name the structures found in the renal hilum.

The structures found in the renal hilum are arteries, veins, ureters, lymphatics, and nerves.

Glossary

Bowman’s capsule
: cup-shaped sack lined by a simple squamous

epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

calyces
: cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

cortical nephrons
: nephrons with loops of Henle that do not extend into the renal medulla

distal convoluted tubules
: portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

efferent arteriole
: arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

glomerulus
: tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

juxtamedullary nephrons
: nephrons adjacent to the border of the cortex

and medulla with loops of Henle that extend into the renal medulla

loop of Henle
: descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

nephrons
: functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

medulla
: inner region of kidney containing the renal pyramids

peritubular capillaries
: second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

proximal convoluted tubules (PCTs)
: tortuous tubules receiving filtrate from Bowman’s capsule; most active part of the nephron in reabsorption and secretion

renal columns
: extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle
: consists of the glomerulus and Bowman's capsule

renal cortex
: outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad
: adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum
: recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae
: medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids
: six to eight cone-shaped tissues in the medulla of the kidney containing collecting

ducts and the loops of Henle of juxtamedullary nephrons

vasa recta
: branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

Microscopic Anatomy of the Kidney
By the end of this section, you will be able to:

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

Nephrons: The Functional Unit

Nephrons take a simple filtrate of the blood and

modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term **forming urine** will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of **renin**), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

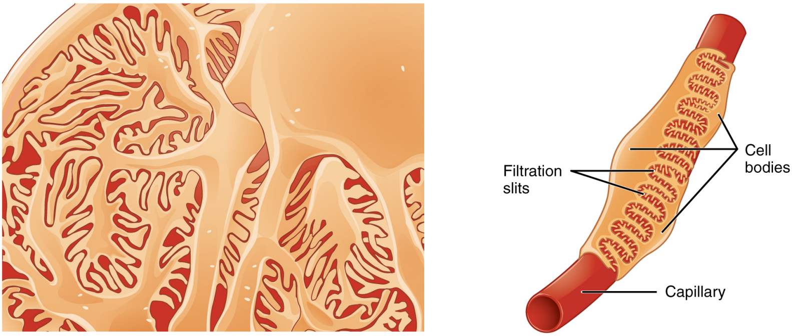
Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (**podocytes**) extending finger-

like arms (**pedicels**) to cover the glomerular capillaries ([link]). These projections interdigitate to form **filtration slits**, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane ([link]). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

Podocytes

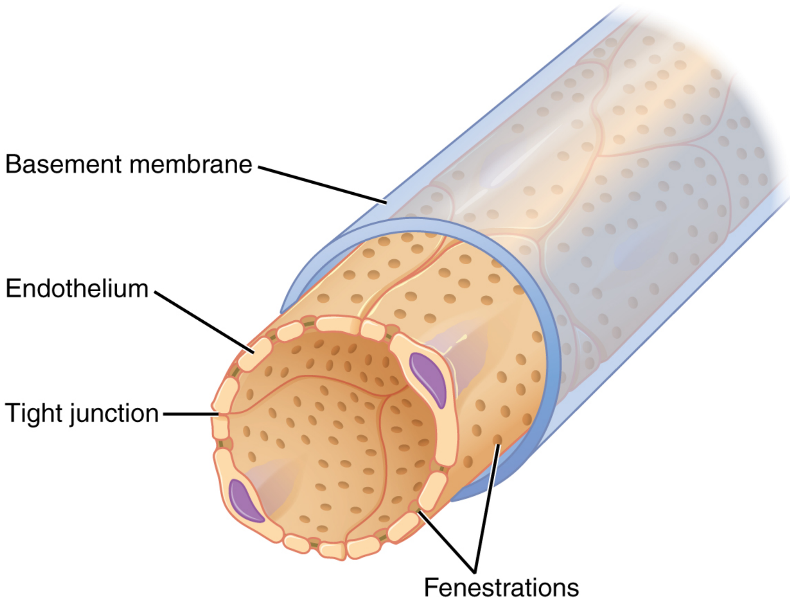
Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.



(a) (b)

Fenestrated Capillary

Fenestrations allow many substances to diffuse from the blood based primarily on size.



The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability

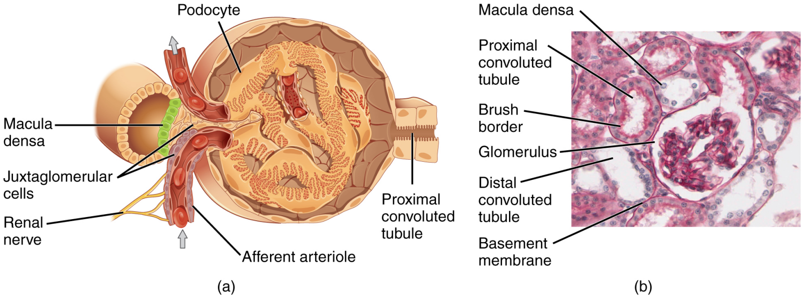
of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** ([link]). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^{+} in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the

tubule. The paracrine signals released in response to changes in flow rate and Na+ concentration are adenosine triphosphate (ATP) and adenosine.

Juxtaglomerular Apparatus and Glomerulus

(a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

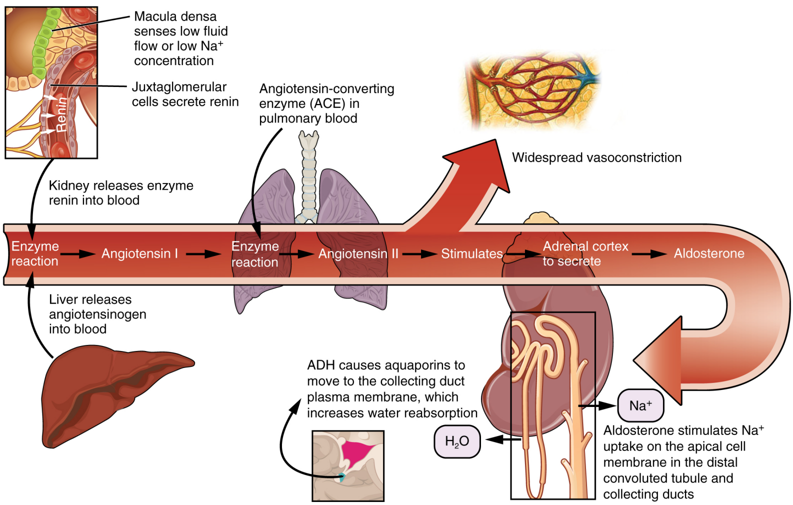


A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax,

increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole ([link]). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from **angiotensinogen** to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na^+ reabsorption by the kidney, which also results in water retention and increased blood pressure.

Conversion of Angiotensin I to Angiotensin II

The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.



Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a **brush border**. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na+, Cl–, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop

of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

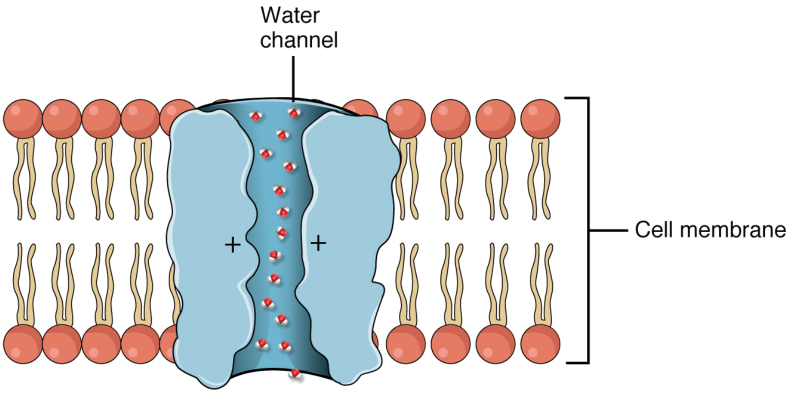
The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane ([link]).

Aquaporin Water Channel

Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.



Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman’s capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure

regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Review Questions

Blood filtrate is captured in the lumen of the _____.

1. glomerulus
2. Bowman’s capsule
3. calyces
4. renal papillae

B

What are the names of the capillaries following the efferent arteriole?

1. arcuate and medullary

2. interlobar and interlobular
3. peritubular and vasa recta
4. peritubular and medullary

C

The functional unit of the kidney is called ______.

1. the renal hilus
2. the renal corpuscle
3. the nephron
4. Bowman's capsule

C

Critical Thinking Questions

Which structures make up the renal corpuscle?

The structures that make up the renal corpuscle are the glomerulus, Bowman's capsule, and PCT.

What are the major structures comprising the filtration membrane?

The major structures comprising the filtration membrane are fenestrations and podocyte fenestra, fused basement membrane, and filtration slits.

Glossary

angiotensin-converting enzyme (ACE)
: enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

angiotensin I
: protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

angiotensin II
: protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

angiotensinogen
: inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to

be activated

aquaporin
: protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

brush border
: formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

fenestrations
: small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

filtration slits
: formed by pedicels of podocytes; substances filter between the pedicels based on size

forming urine
: filtrate undergoing modifications through secretion and reabsorption before true urine is produced

juxtaglomerular apparatus (JGA)
: located at the juncture of the DCT and the afferent and efferent arterioles of the

glomerulus; plays a role in the regulation of renal blood flow and GFR

juxtaglomerular cell
: modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

macula densa
: cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

mesangial
: contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

pedicels
: finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

podocytes
: cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

renin
: enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the

conversion of angiotensinogen into angiotensin I

Tubular Reabsorption

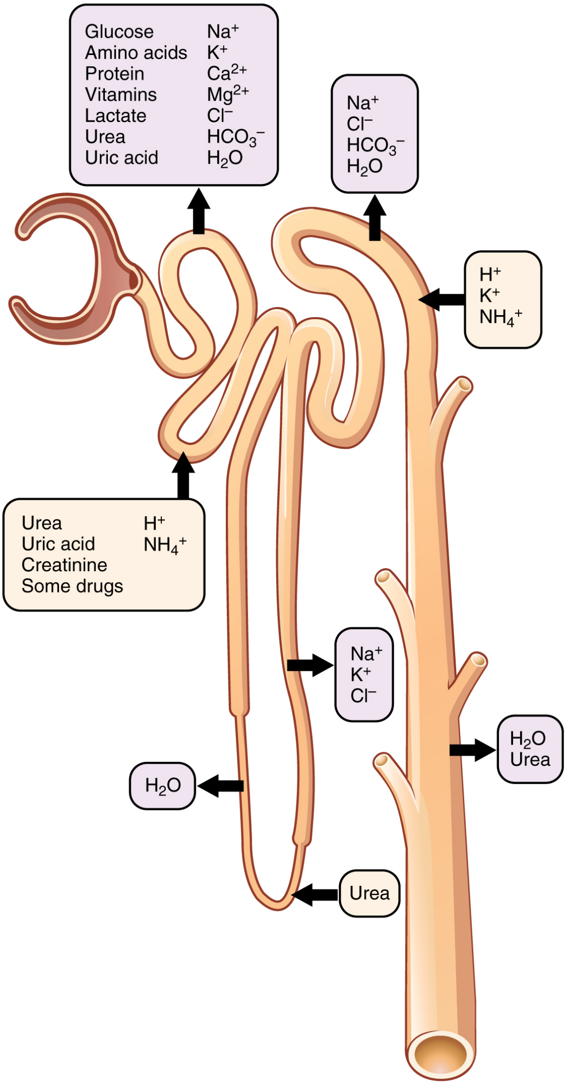
By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts ([link] and [link]). Various portions of the nephron differ in their

capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

Locations of Secretion and Reabsorption in the Nephron


Glucose
Amino acids
Protein
Vitamins
Lactate
Urea
Uric acid
Na^+
K^+
Ca^{2+}
Mg^{2+}
Cl^-
HCO_3^-
H_2O
Na^+
Cl^-
HCO_3^-
H_2O
H^+
K^+
NH_4^+
Urea
Uric acid
Creatinine
Some drugs
H^+
NH_4^+
Na^+
K^+
Cl^-
H_2O
Urea
H_2O
Urea

Substances

Secreted or Reabsorbed in the Nephron and Their Locations

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na +			
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na +			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			
Urea	50 percent reabsorbed by diffusion;	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts;

	also secreted			diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
Bicarbonate	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport		Reabsorbed antiport with Cl^-

		with Cl^-; in ascending limb		
H^+	Secreted; diffusion		Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
HCO_3^-	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with Na^+
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending	Reabsorbed	

		limb; diffusion		
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of Na^+ out of a cell and K^+ into a cell by the Na^+/K^+ pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations, Na^+ ions, is an example of facilitated diffusion. In some cases of mediated transport, two different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. As described previously, when active transport powers the transport of another substance in this way, it is called “secondary active transport.” Glucose reabsorption in the kidneys is by secondary active transport. Na^+/K^+ ATPases on the basal membrane of a tubular cell constantly pump Na^+ out of the cell, maintaining a strong electrochemical gradient for Na^+ to move into the cell from the tubular lumen. On the luminal (apical) surface, a Na^+/

glucose symport protein assists both Na^+ and glucose movement into the cell. The cotransporter moves glucose into the cell against its concentration gradient as Na^+ moves down the electrochemical gradient created by the basal membranes Na^+/K^+ ATPases. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

Most of the Ca^{++}, Na^+, glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, K^+, ammonia (NH_3), creatinine, and some drugs are secreted into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^+, whereas the kidneys secrete or reabsorb H^+ and HCO_3^- ([link]). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

Substances Filtered and

Reabsorbed by the Kidney per 24 Hours

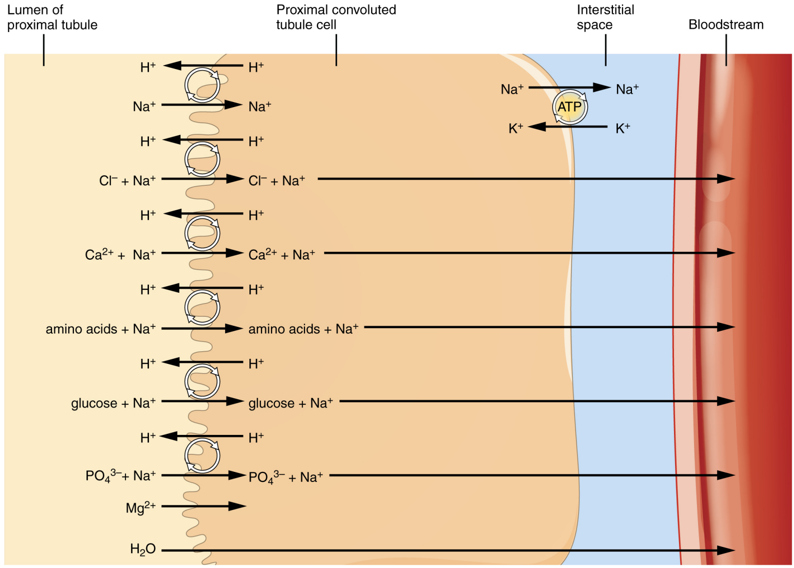
Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Water	180 L	179 L	1 L
Proteins	10–20	10–20	0
Chlorine	630	625	5
Sodium	540	537	3
Bicarbonate	300	299.7	0.3
Glucose	180	180	0
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the

term “reabsorbed.” All of these substances were “absorbed” in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is “obliged” to follow the Na^+ ([link]).

Substances Reabsorbed and Secreted by the PCT



More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with Na+. Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary

between the apical and basilar surfaces. A few of the substances that are transported with Na^+ (symport mechanism) on the apical membrane include Cl^-, Ca^{++}, amino acids, glucose, and PO_4^{3-}. Sodium is actively exchanged for K^+ using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions, K^+, Ca^{++}, and Mg^{++}, diffuse laterally between adjacent cell membranes (transcellular).

About 67 percent of the water, Na^+, and K^+ entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or T_m). In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of **glycosuria** usually points to type I or II diabetes mellitus. The transport of glucose from the lumen of the PCT to the interstitial space is similar to the way it is absorbed

by the small intestine. Both glucose and Na^+ bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it. Na^+ is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the Na^+/K^+ ATPase that pumps Na^+ out of the cell on the basal surface. Fifty percent of Cl^- and variable quantities of Ca^{++}, Mg^{++}, and HPO_4^{2-} are also recovered in the PCT.

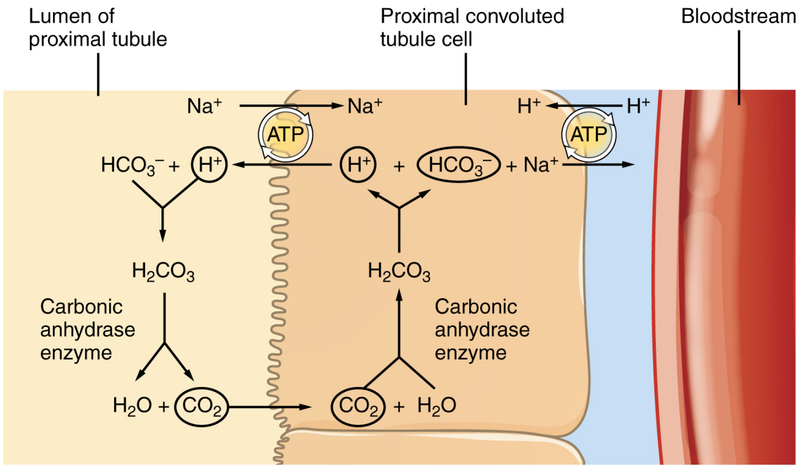
Recovery of bicarbonate (HCO_3^-) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of CO_2, in the stomach to produce hydrochloric acid, and in the pancreas to produce HCO_3^- to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT, HCO_3^- combines with hydrogen ions to form carbonic acid (H_2CO_3). This is enzymatically catalyzed into CO_2 and water, which diffuse across the apical membrane into the cell. Water can move

osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions (HCO_3^-). These bicarbonate ions are cotransported with Na^+ across the basal membrane to the interstitial space around the PCT ([link]). At the same time this is occurring, a Na^+/H^+ antiporter excretes H^+ into the lumen, while it recovers Na^+. Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a Na^+ gradient is created by the Na^+/K^+ pump.

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

Reabsorption of Bicarbonate from the PCT



Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na+ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100

mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na^+, and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

The ascending loop is made of very short thin and

longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+ and CL^-, are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hypoosomotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

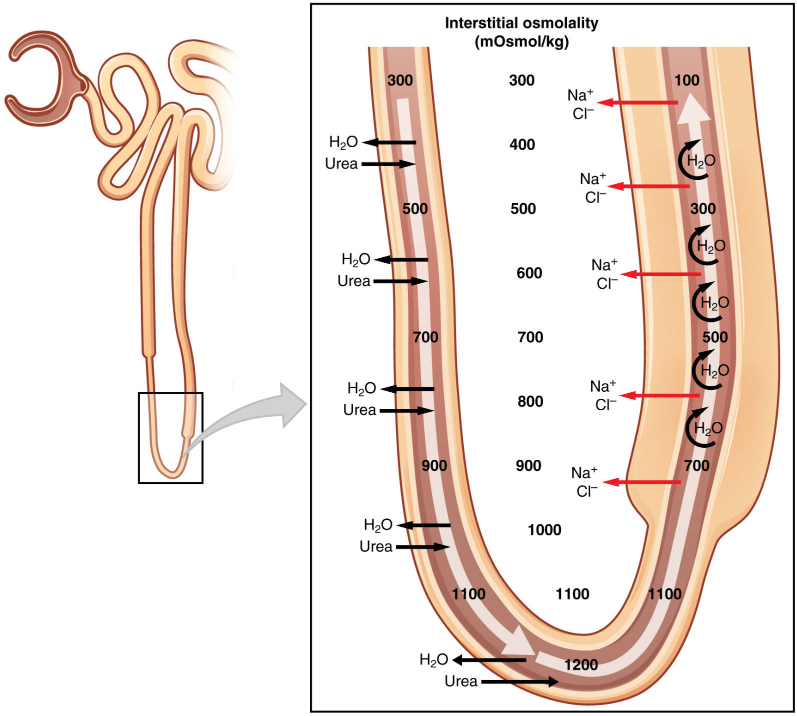
The Na^+/K^+ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl^- by Na^+/Cl^- symporters in the apical membrane. At the same time that Na^+ is actively pumped from the basal side of the cell into the interstitial fluid, Cl^- follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the “back door exiting” K^+, there is one Na^+ and two Cl^- ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the

lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na^+, K^+, Ca^{++}, and Mg^{++}) from the lumen via a paracellular route to the interstitial space and vasa recta.

Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system** ([link]). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na^+ deep in the medulla.

Countercurrent Multiplier System



As discussed above, the ascending loop actively reabsorbs NaCl out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of NaCl to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia (NH_3) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, NH_2, is removed from amino acids as they are broken down. Most of the resulting

ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of Na^+ and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and Na^+ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As NH_2 from the amino acid is converted into NH_3 and pumped into the lumen of the PCT, Na^+ and HCO_3^- are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid NH_4^+) in the urine and a gain of a bicarbonate ion (HCO_3^-) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave the loop and enter the

hyperosmolar interstitium of the pyramid, where it is returned to the circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $Na^+/K^+/2Cl^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na^+ and urea, destroying the

osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na^+ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters and is removed.

Watch this video to learn about the countercurrent multiplier system.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine

enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na^+/K^+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na^+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl^- out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca^{++} from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca^{++} recovery from the forming urine. In addition, as Na^+ is pumped out of the cell, the resulting electrochemical gradient attracts Ca^{++} into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport Ca^{++} into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{++} not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity

decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na^+ is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume

(water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates Na^+ recovery. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is recovered from the forming urine and water follows the Na^+ passively. As the pump recovers Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is recovered in the circulation. Symport channels move Na^+ and Cl^- together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the recovery of Na^+.

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and HCO_3^- while secreting H^+. This function lowers the acidity of the plasma while increasing the acidity of the urine.

Chapter Review

The kidney regulates water recovery and blood

pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body's fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH_3, creatinine, and some drugs are filtered or secreted as wastes. H^+ and HCO_3^- are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate (HCO_3^-) is recovered using the same enzyme, carbonic anhydrase (CA), found in

erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtaglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers Na^+, reducing filtrate osmolarity to 50–100 mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase Na^+ concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates Na^+ recovery by the collecting duct.

Review Questions

Aquaporin channels are only found in the collecting duct.

1. true
2. false

B

Most absorption and secretion occurs in this part of the nephron.

1. proximal convoluted tubule
2. descending loop of Henle
3. ascending loop of Henle
4. distal convoluted tubule
5. collecting ducts

A

The fine tuning of water recovery or disposal occurs in _____.

1. the proximal convoluted tubule
2. the collecting ducts
3. the ascending loop of Henle
4. the distal convoluted tubule

B

Critical Thinking Questions

Which vessels and what part of the nephron are involved in countercurrent multiplication?

The vasa recta and loop of Henle are involved in countercurrent multiplication.

Give the approximate osmolarity of fluid in the proximal convoluted tubule, deepest part of the loop of Henle, distal convoluted tubule, and the collecting ducts.

The approximate osmolarities are: CT = 300; deepest loop = 1200; DCT = 100; and collecting ducts = 100–1200.

Glossary

countercurrent multiplier system
: involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

glycosuria
: presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus

intercalated cell
: specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate; important in acid–base balance

leaky tight junctions
: tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes

principal cell
: found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

The Urinary System and Homeostasis
By the end of this section, you will be able to:

- Describe the role of the kidneys in vitamin D activation
- Describe the role of the kidneys in regulating erythropoiesis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

In order for vitamin D to become active, it must

undergo a hydroxylation reaction in the kidney, that is, an –OH group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of Ca^{++} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{++} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{++} leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell.

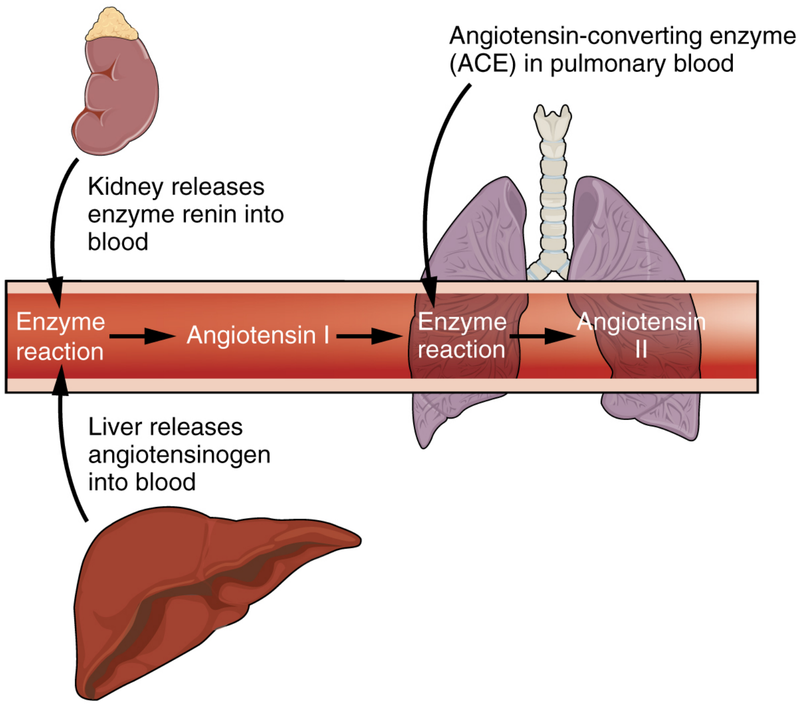
One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

Blood Pressure Regulation

Due to osmosis, water follows where Na^+ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na^+. ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic dieresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (see [link]). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II ([link]). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of Na^+ and its associated osmotic recovery of water. The reabsorption of Na^+ helps to raise and maintain blood pressure over a longer term.

The Enzyme Renin Converts the Pro-enzyme Angiotensin



Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum

osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death) .

Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of Na^+ and Ca^{++} homeostasis has been discussed at length. Failure of K^+ regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its

function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

Everyday Connection

Stem Cells and Repair of Kidney Damage

Stem cells are unspecialized cells that can reproduce themselves via cell division, sometimes after years of inactivity. Under certain conditions, they may differentiate into tissue-specific or organ-specific cells with special functions. In some cases, stem cells may continually divide to produce a mature cell and to replace themselves. Stem cell therapy has an enormous potential to improve the quality of life or save the lives of people suffering from debilitating or life-threatening diseases. There have been several studies in animals, but since stem cell therapy is still in its infancy, there have been limited experiments in humans.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

Chapter Review

The effects of failure of parts of the urinary system may range from inconvenient (incontinence) to fatal (loss of filtration and many others). The kidneys catalyze the final reaction in the synthesis of active vitamin D that in turn helps regulate Ca^{++}. The kidney hormone EPO stimulates erythrocyte development and promotes adequate O_2 transport. The kidneys help regulate blood pressure through Na^{+} and water retention and loss. The kidneys work with the adrenal cortex, lungs, and liver in the renin–angiotensin–aldosterone system to regulate blood pressure. They regulate osmolarity of the blood by regulating both solutes and water. Three electrolytes are more closely regulated than others: Na^{+}, Ca^{++}, and K^{+}. The kidneys share pH regulation with the lungs and plasma buffers, so

that proteins can preserve their three-dimensional conformation and thus their function.

Review Questions

Which step in vitamin D production does the kidney perform?

1. converts cholecalciferol into calcidiol
2. converts calcidiol into calcitriol
3. stores vitamin D
4. none of these

B

Which hormone does the kidney produce that stimulates red blood cell production?

1. thrombopoeitin
2. vitamin D
3. EPO
4. renin

C

If there were no aquaporin channels in the collecting duct, ______.

1. you would develop systemic edema
2. you would retain excess Na^+
3. you would lose vitamins and electrolytes
4. you would suffer severe dehydration

D

Critical Thinking Questions

How does lack of protein in the blood cause edema?

Protein has osmotic properties. If there is not enough protein in the blood, water will be attracted to the interstitial space and the cell cytoplasm resulting in tissue edema.

Which three electrolytes are most closely regulated by the kidney?

The three electrolytes are most closely regulated by the kidney are calcium, sodium,

and potassium.

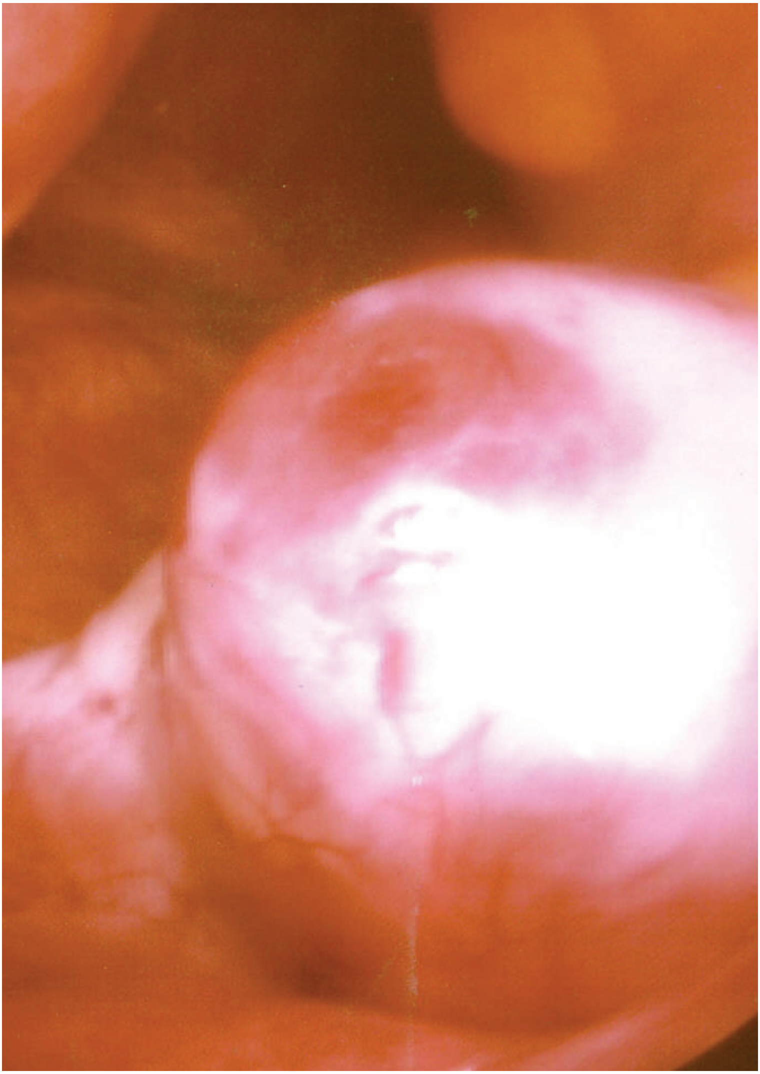
References

Bagul A, Frost JH, Drage M. Stem cells and their role in renal ischaemia reperfusion injury. Am J Nephrol [Internet]. 2013 [cited 2013 Apr 15]; 37(1):16–29. Available from: http://www.karger.com/Article/FullText/345731

Glossary

osteomalacia
: softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

Introduction
class="introduction"
Ovulation
Following a surge of luteinizing hormone (LH), an oocyte (immature egg cell) will be released into the uterine tube, where it will then be available to be fertilized by a male's sperm. Ovulation marks the end of the follicular phase of the ovarian cycle and the start of the luteal phase.



Chapter Objectives

After studying this chapter, you will be able to:

- Describe the anatomy of the male and female

reproductive systems, including their accessory structures
- Explain the role of hypothalamic and pituitary hormones in male and female reproductive function
- Trace the path of a sperm cell from its initial production through fertilization of an oocyte
- Explain the events in the ovary prior to ovulation
- Describe the development and maturation of the sex organs and the emergence of secondary sex characteristics during puberty

Small, uncoordinated, and slick with amniotic fluid, a newborn encounters the world outside of her mother's womb. We do not often consider that a child's birth is proof of the healthy functioning of both her mother's and father's reproductive systems. Moreover, her parents' endocrine systems had to secrete the appropriate regulating hormones to induce the production and release of unique male and female gametes, reproductive cells containing the parents' genetic material (one set of 23 chromosomes). Her parent's reproductive behavior had to facilitate the transfer of male gametes—the sperm—to the female reproductive tract at just the right time to encounter the female gamete, an oocyte (egg). Finally, combination of the gametes (fertilization) had to occur, followed by

implantation and development. In this chapter, you will explore the male and female reproductive systems, whose healthy functioning can culminate in the powerful sound of a newborn's first cry.